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THE NEWER PHYSIOLOGY OF THE GASTROINTESTINAL TRACT.

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In this paper I desire to outline the known causes and mechanism of the gastric and pancreatic secretory response to a meal and to briefly summarize the recent advances that have been made in other fields of gastroenterology.

Gastric Secretion. The gastric secretory response to a meal can be divided into three phases with reference to the site at which the stimuli are acting: (1) The cephalic phase; (2) the gastric phase; and (3) the intestinal phase.

The Cephalic Phase. It is well established that the sight, smell and taste of food in the presence of appetite causes the secretion of gastric juice. The nervous impulses go to the stomach via the vagi.[1] According to Zoliony, a decerebrate dog will secrete gastric juice on sham feeding.[2] This proves that other than solely cerebral reflexes are concerned in the excitation of the gastric glands from the head region. It is certain, then, that the cephalic phase of gastric secretion is caused by (*a*) reflexes through the cerebral cortex (psychic), and by (*b*) reflexes through the thalamus, midbrain or medulla, the vagi being the sole pathway of the excitatory impulses.

The Gastric Phase. In order to study this phase without the introduction of complicating factors, we made a pouch of the entire stomach, reëstablishing the continuity of the gut by a duodeno-esophageal end-to-end anastomosis.[3]

Mechanical Stimulation by Distention. We have found that when a balloon is placed in the pouch of the entire stomach and distended with from 150 to 300 cc. of air, the gastric glands are caused to secrete after a latent period of from five to fifteen minutes. When this stimulus is applied for half an hour from 20 to 50 cc. of the juice of high acidity is produced. The stomach of man also responds to distention, unless inhibitory factors are caused to operate.[3]

Chemical Stimulation by Application of Substances to the Gastric Mucosa. We have applied the common foods to the gastric mucosa in quantities insufficient to stimulate mechanically. We found that meat or meat juice is the only common food substance that stimulates on local application to the gastric mucosa. Histamin and B-alanin are pure chemical substances which stimulate on local gastric application.[3]

These observations show that the gastric phase of gastric secretion is caused by (*a*) mechanical distention of the stomach and by (*b*) the action on or by way of the gastric mucosa of substances in the food.

THE INTESTINAL PHASE. When a dog with a pouch of the entire stomach and a duodeno-esophageal anastomosis is fed a meal, two to four hours later the stomach begins to secrete copiously. If the meal is predigested, copious secretion begins within an hour. It is evident that in such an animal the food passes directly into the intestine from the esophagus. Therefore, the only way to account for the secretion is that it is due to the food or its digested products acting in the intestine.[4]

Since distention of the intestine does not stimulate the gastric glands, we believe that the intestinal phase of gastric secretion is due to chemical substances in the food or, preferably, that arise from digestive, and possibly bacterial action, in the intestine, which act on or by way of the intestinal mucosa.

MECHANISM. We are quite certain that several mechanisms are concerned in the secretion of gastric juice. These mechanisms are: (1) Secretory nerves; (2) increased blood flow, and (3) humoral agents. Space does not permit a discussion of the evidence supporting the first two mechanisms, but we will consider the evidence proving a humoral mechanism.

A Humoral Mechanism for Gastric Secretion. We first attempted to prove a humoral mechanism for gastric secretion by blood transfusion and long-time cross-circulation experiments. These procedures did not yield satisfactory proofs.[5]

By a method described elsewhere we were successful in transplanting a pouch of the stomach under the mammary gland.[6] We found that when the dog was fed the transplanted pouch of the stomach secreted gastric juice. This proved unequivocally that when a meal is ingested something enters the blood stream that stimulates the gastric glands. This humoral agent must be either a hormone, or secretagogues, or both.

Pancreatic Secretion. The external secretion of the pancreas is without doubt the most important of the digestive secretions. Yet, less is known concerning the physiology of its production than of the physiology of the production of gastric juice. We have been and are at present attempting to study and analyze the causes and mechanism concerned in the secretion of pancreatic juice by methods similar to those we have used for the study of the secretion of gastric juice. Our observations indicate that the pancreatic secretory response to a meal can be divided into two phases with reference to the site at which the stimuli are acting: (1) The cephalic phase, and (2) the intestinal phase, there being no gastric phase.

THE CEPHALIC PHASE. We have repeated and confirmed Pawlow's experiments on sham-feeding a dog with a chronic pancreatic fistula.[1] The amount of secretion that results from the sight, smell and taste of food is small, amounting to only 2 cc. in fifteen minutes.

THE GASTRIC PHASE. To determine whether or not food or acid in the stomach causes the pancreas to secrete, we used a dog with a pouch of the entire stomach and a duodeno-esophageal anastomosis. A duodenal tube was passed by mouth into the duodenum for collecting secretions. We found that when various substances (acid, fat meat extract, water, and so forth) were placed in the pouch of the entire stomach no augmentation of flow of secretion from the duodenal tube resulted.

From these negative results we are lead to believe that there is no gastric phase of pancreatic secretion.

THE INTESTINAL PHASE. There being no gastric phase and the cephalic phase being so small that it is not important, the intestinal phase of pancreatic secretion is the most important phase of the external secretory activity of the pancreas. It has been definitely established that acids, neutral fats, fatty acids, soaps, proteins (meat, not egg-white), starch, alcohol, and water, stimulate external pancreatic secretion when introduced into the stomach so that they may enter the intestine. How these substances stimulate has not been definitely ascertained. Several possible mechanisms have been suggested. These mechanisms are as follows: (*a*) These substances, on coming into contact with the upper intestinal mucosa, excite local reflexes to the pancreas which exert either a specific secretory influence on the pancreatic cells, or cause an increase in blood flow through the pancreas. (*b*) These substances either contain, or on digestion yield, secretagogues that stimulate either by local reflexes, or after being absorbed into the blood, by action on the pancreatic cells or their blood supply. (*c*) These substances, or secretagogues which might be present in them, on coming into contact with the upper intestinal mucosa, cause a hypothetical substance, "prosecretin," present in the cells of the mucosa, to be converted into "secretin," an alleged hormone, which passes into the blood and is carried to the pancreas and stimulates it, either by direct action on the

cells or by causing an increased blood flow and capillary permeability, this being the mechanism that is commony known as the Bayliss and Starling secretin theory. (*d*) These substances may effect the motility of the upper intestine which in turn, by reflexes or by an increase in blood flow, may excite the pancreas. Also a change in motility may play an indirect role by promoting the absorption of secretagogues, or the passage of a hormone stored in the mucosal cells, into the blood. Any one or all of these possible mechanisms, must be considered in analyzing how any single substance excites the pancreas to external secretion when introduced into the intestine.

A Humoral Mechanism for Pancreatic Secretion. A humoral mechanism for external pancreatic secretion has not been established. However, work has been done which has suggested that such a mechanism does exist, at least for acid stimulation.

Recently we have devised a method for transplanting the entire tail of the pancreas subcutaneously into the mammary gland.[7] A two-stage operation was employed similar to that used by us for transplanting a pouch of the stomach subcutaneously. The transplant is entirely severed from its original blood and nerve supply. It receives blood only from the vessels that supply the mammary gland and closely adjacent structures. The transplant always takes, if a dog that has recently whelped or weaned pups is used in order to insure a vascular bed. As calculated from the amount of secretion that the transplant should theoretically produce, approximately 50 per cent of the gland transplant undergoes atrophy. But sufficient gland tissue remains to render this preparaton an ideal test object for the study of many problems related to both the external and internal secretory function of the pancreas.

These transplants persist indefinitely. One is on hand now that was made one year ago. We (Farrell and Ivy) have removed the remainder of the pancreas and have found that the animal remains sugar-free on a meat diet and, that the carbohydrate tolerance, though less than normal, remains constant, constituting, we believe, a beautiful preparation for studies on problems related to diabetes.

Such a pancreatic transplant secretes a continuous secretion and is definitely excited to secrete after a meal, 6 cc. of juice having been collected in one hour. This fact unequivocally established a humoral mechanism for pancreatic secretion, because the only manner by which the transplant could be so excited would be by substances carried to it via the blood stream.[8]

This experiment does not reveal the nature of the substance, or substances, that gets into the blood. In other words, it does not show whether secretagogues in the food, or produced by digestion, are the exciting substances, or whether a hormone, or hormones, is responsible for the stimulation.

THE PROOF OF A HORMONE FOR EXTERNAL PANCREATIC SECRETION. Attempts have been made to demonstrate the presence of a

hormone in the circulating blood of animals after the introduction of acid into the lumen of the intestine. Wertheimer and Lepage,[9] also Fleig,[10] collected the venous blood from the jejunum and injected it into another animal with the result that the animal's pancreas was caused to secrete. Enriquez and Hallion[11] obtained a similar result from blood taken from the carotid. Popielski states that an increase in pancreatic secretion can be elicited by the injection of blood from a nonsecreting or control dog. Matsuo[12] obtained positive results in 4 out of 8 experiments in which he did an acute carotid-to-jugular cross-circulation, obviously an unphysiological type of cross-circulation. Luckhardt,[13] using a syringe-cannula method obtained negative results on cross-circulating a secreting with a nonsecreting animal. Recently Ivy, Lim and McCarthy have found blood transfusion and cross-circulation experiments inadequate for determining whether or not a humoral mechanism is concerned in gastric secretion.[5]

We (Ivy and Farrell) have attempted to solve the problem by making the two following animal preparations: (1) A Thiry fistula of the jejunum was made in a dog that had a pancreatic transplant; (2) a 12-inch loop of jejunum was transplanted under the skin of another dog and at a later date a pancreatic transplant was made.[14]

It was found that when either one-tenth normal or one-hundredth normal HCl was applied to the intestinal mucosa of the loop, the pancreatic transplant would secrete copiously within four to six minutes after beginning the application. In other words, the application of a pure chemical substance to the intestinal mucosa—food and cellular detritus absent—caused the mucosa to give off something, a hormone, to the blood stream which excited the cells of the pancreatic transplant to secrete.

This, we believe, is the first unequivocal proof that a hormone may be one of the mechanisms concerned in the external secretory response of the pancreas to a meal.

It is still necessary for us to show that such a mechanism operates normally. That such a mechanism operates normally has been questioned recently by McClure[15] and his associates on the evidence that the gastric chyme is rapidly neutralized in the duodenum and that the pH of duodenal contents varies from 3 to 8. This is not sufficient evidence to rule out entirely the possibility that acid chyme is causing the production of a hormone. Also, it must be kept in mind that acid chyme is being intermittently ejected into the duodenum—every three to ten seconds—and that there are brief periods, even though each period may be less than a minute in duration, of acid contact with the proximal duodenal mucosa, which when summed up may be sufficient to cause the production of a hormone.

OTHER MECHANISMS. A hormone mechanism cannot explain all of the known facts of the causes of the intestinal phase of external pancreatic secretion.

Using the Thiry-fistula-pancreatic-transplant preparation referred to above, we have found that when fresh olive oil is applied to the intestinal mucosa, either no, or a very slight amount of, stimulation of the transplant occurs. But, if we digest the olive oil with pancreatin for several days and then neutralize the acidity developed (fatty acids) and apply it to the intestinal mucosa the pancreatic transplant secretes.

Since it is known that olive oil introduced into the duodenum of a pancreatic fistula dog stimulates within a period of time (five minutes) in which it would be unreasonable to assume that appreciable digestion would have occurred, it seems very likely that olive oil stimulates on contact with the mucosa by exciting local reflex mechanisms.

We have also found that when bile is applied to the intestinal mucosa the transplant is caused to secrete. This is significant because bile passes into the intestine during a meal in sufficient quantities to stimulate the pancreas.

It should be clear from this brief discussion that several mechanisms are concerned in the causation of the intestinal phase of pancreatic secretion. A hormone is not the sole mechanism. Several mechanisms exist—factors of safety, if you please—that can arouse pancreatic secretion in achylia gastrica or in conditions in which the chyme ejected into the duodenum is not acid in reaction.

Motor Activity. The generally accepted idea regarding the effect of the vagus and splanchnic nerves on the gastrointestinal tract has been that the vagus carries inhibitory and the splanchnic motor impulses to the cardiac and pyloric sphincters, even though the reports in the literature varied. Carlson and Litt[16] have shown that the response of these sphincters to nerve stimulation and to drugs depends upon the physiological condition of the sphincters at the time the stimulus is applied. If the sphincters are relaxed, the stimulus causes contraction; if the sphincters are contracted, the sphincters are caused to relax. This observation has been confirmed by Thomas[17] and explains the discordant results reported in the experimental and clinical literature. It also shows that cardiospasm, or pyloric spasm, may be due to reflexes over either the vagi or splanchnic nerves.

It was formerly believed that reverse or antiperistalsis normally occurred only in the proximal colon and abnormally in the stomach in vomiting. We know from the observations of Alvarey, Wheelon,[18] Keeton, Spencer, Carlson, and the writer that antiperistalsis may occur in any portion of the gastrointestinal tract. Carlson[19] has recently observed it in the esophagus in a case of esophageal stricture.

Carlson and Luckhardt[20] have presented evidence that hunger

contractions are due to some change in the blood. Recently we[21] have shown that a transplanted gastric pouch shows hunger periods simultaneously with the stomach proper, evidence which unequivocally proves that hunger contractions are due to some humoral agency. It has been shown by Bulato and Carlson[22] that sugar metabolism is in some way related to the humoral agency, since glucose injected intravenously stops hunger contractions and insulin administration increases hunger contractions.

Absorption. Although normally most proteins are reduced to amino-acids before being absorbed from the intestine, there are at least two protein substances that are absorbed normally from the intestine without being digested. One of these is thyroglobulin, which Hektoen has detected by immunologic methods in the blood after feeding it.[23] The other is tissue fibrinogen, as prepared by Mills.[24] Mills has found that tissue fibrinogen, a substance that causes coagulation of blood, can be given by mouth, causing the coagulation time of blood to decrease for several hours, and then obtained unchanged in the urine. It is well known that under certain abnormal conditions undigested protein may be absorbed from the intestine. Hettwer and Kriz[25] have recently made an additional contribution by finding that increased intraintestinal pressure caused by intestinal stasis may result in a sufficiently rapid absorption to cause anaphylactic shock in sensitive guinea-pigs.

The Biliary Passages. Recent investigations have at least proven that the gall bladder has one function, namely, concentration of the bile.[26] It also probably plays a role in the regulation of the intrabiliary duct pressure. That this is an important function in those animals that have a gall bladder is shown by the fact that the common bile duct dilates after removal of the gall bladder. Because of the small amount of smooth muscle in the wall of the gall bladder, it is probably more correct to say that the gall bladder evacuates rather than contracts.

I would like to emphasize the point that very probably the most important factor controlling the outflow of bile from the gall bladder and biliary passages is the motility and tonus of the duodenum. This has been pointed out clearly by Burget.[27]

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OBSERVATIONS ON GASTRIC FUNCTION IN DIGESTIVE DISORDERS.

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With the introduction of clinical methods of gastric analysis many years ago, it was hoped that diagnostic information of value in differentiating various disorders of the stomach would be forthcoming. The results at first seemed very encouraging and various syndromes based on studies of test meal findings were soon described. However, as time has gone by it has become evident that such supposed diseases as hyperacidity or anacidity have no very uniform pathologic basis and that great variations in gastric activity may occur in apparently normal people. Most clinicians at the present time hesitate to make an exact diagnosis from the results of gastric analysis alone.

During the past winter we have examined a series of people both with and without gastric disorders by means of a procedure,[1] which makes it possible to estimate simultaneously the volume of stomach secretions, the acidity of the pure gastric juice and the emptying time of the stomach. Our purpose was to determine critically the diagnostic possibilities of gastric functional studies. The findings in the controls have already been described;[2] the present paper deals with the results obtained in a series of people suffering from digestive disturbances.

Material. The material studied may be classified as follows:

1. Gastric and duodenal ulcer: There were 13 cases, 11 of which

were verified. The group was a miscellaneous one and included patients of various ages and types. In 1 case there was marked pyloric obstruction.

2. Cancer of stomach: Four cases, all advanced, verified by operation or autopsy.

3. Cholelithiasis: Five instances, all with definite biliary colic; all verified.

4. Cancer of abdominal organs other than stomach: Five cases, all verified; 2 primary cancer of liver, 2 cancer of pancreas, 1 cancer of bile ducts.

5. Miscellaneous abdominal disease: Six cases; chronic amebic dysentery, ulcerative colitis, polyposis of colon, volvulus of ileum, encapsulated peritonitis.

6. Psychoneurosis: Four cases; psychoneurotic individuals with outstanding complaint of indigestion but no evidence of abdominal disease.

A large number of cases in which the diagnosis was uncertain are not included in the present report.

Methods. The method used in studying gastric activity has been described in detail elsewhere and reference may be made to the former paper.[1] A complete protocol of a single examination is inserted here (Table I and Chart I) for reference; otherwise only a summary of the results is charted.

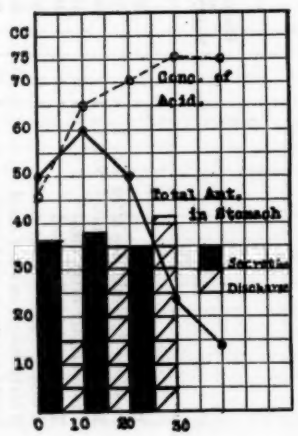


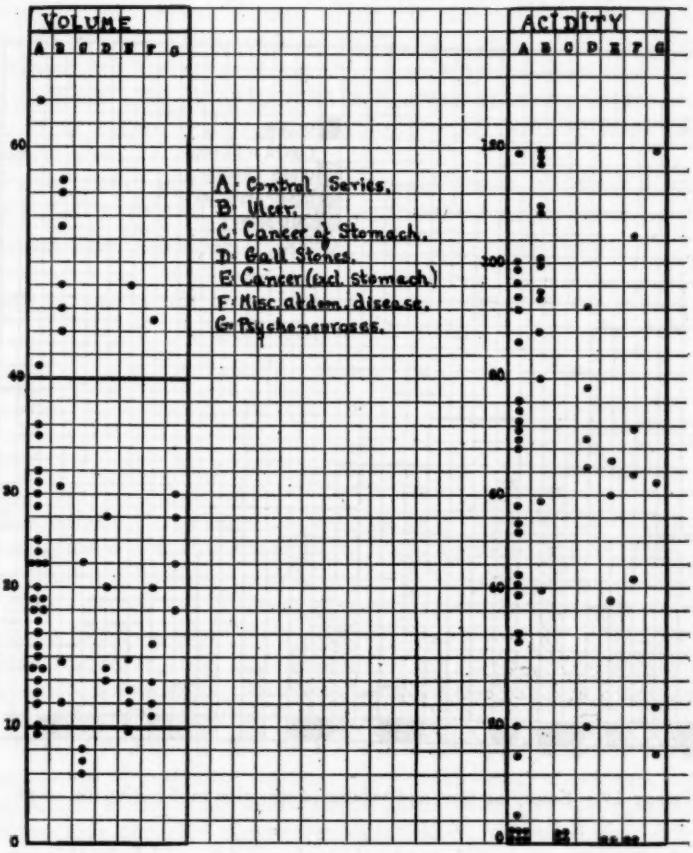
CHART I.—Findings in a normal individual.

The Volume of Gastric Secretion. In Column A of Chart II is shown the average ten-minute volume of gastric secretion in a series of controls without abdominal disorder. It is seen that with occasional exceptions the figure varies from 10 to 40 cc. In column B are shown the secretion volumes of 9 cases of gastric or duodenal

TABLE I.—SUMMARY OF FINDINGS IN A NORMAL INDIVIDUAL.

Specimen number.		pH.	Dimethyl, cc., N/10NaOH.	Phenol phthalein, cc., N/10NaOH.	Total Amount in stomach, cc.	Amount retained, cc.	Amount returned, cc.	Phthalein reading, per cent.	Amount secreted, cc.	Amount discharged, cc.
1.	Fasting	1.2	52	66						
2.	Fasting, five minutes after No. 1	1.1	52	66						
3.	Fasting, ten minutes after No. 1	1.1	66	78						
4.	Immediately after meal	1.9	10	14	50	10	40	72		
5.	Ten minutes after meal	1.4	40	42	60	12	48	32	35.5	15
6.	Twenty minutes after meal	1.2	52	60	50	10	40	16	37.5	35
7.	Thirty minutes after meal	1.15	62	72	22	10	12	6	35.0	43
8.	Forty minutes after meal	1.15	62	74	14	..	..	Trace		

ulcer in which satisfactory determinations were made. The large volumes of secretion obtained in 6 of the 9 cases are striking in contrast to all the other groups both normal and abnormal. It is to be noted, however, that in some of the ulcer cases, which differed in no important clinical particular from the others, the secretion was scanty. Column C shows the results in 4 cases of cancer of stomach. In 3 of these the volumes are distinctly subnormal; in



CHARTS II and III.—Secretion volume and acidity in normal and abnormal cases.

the fourth the volume was normal but not high. In the remaining four groups (D, E, F and G) the volumes all are within normal limits.

In summary, then, it may be said that the only deviation from normal which was found was the tendency to large volumes of secretion in the ulcer cases and to subnormal volumes in the instances of cancer of stomach.

The Acidity of the Gastric Juice. Column A (Chart III) shows the highest acidity of the gastric juice reached during the test (which continues over a period of approximately one hour after stimulation) in a series of controls. As we have pointed out before, there is every degree of acidity, from 0 (titratable) up to 120, although acidities of over 100 are uncommon in normal people. In column B are shown the results in 13 cases of ulcer. The well-known tendency to high acid values is brought out in contrast to

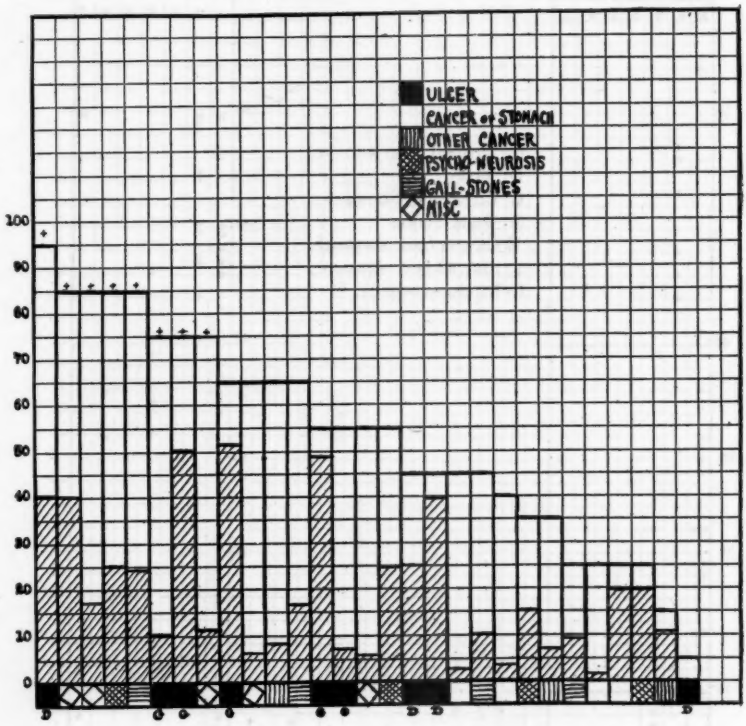


CHART IV.—Emptying time and volume of secretion in digestive disorders.

the findings in cancer of stomach (column C), which in this small series invariably showed an anacidity. In the remaining groups (D, E, F, G) there was obviously no relation between the type of disorder and the degree of acidity.

Gastric Motility. In the previous paper on gastric act vity in normal people the great variations in motility of the stomach found in the various members of the group and in the same persons at different examinations were stressed. The emptying time of the stomach was found to vary over a range of from ten to ninety or

more minutes following a constant stimulus under standard conditions. Furthermore, the emptying time bore no significant relation to the volume of gastric secretion. The emptying time (minutes) in the present series of abnormal cases is shown in Chart IV. Each column indicates the emptying time in a single case, the shaded columns show the ten-minute volume of secretion (cc.) and the key at the bottom indicates the type of disease. It is immediately apparent that, just as with the controls, great variations in motility obtain in the present group. There is also no distinct relation between emptying time and any particular disease, although it may be noted that the stomach on the whole emptied more quickly in the duodenal than in the gastric ulcer cases. However, no information of any definite diagnostic value is to be deduced from these observations.

Furthermore, just as with the normal group, there were very often great variations in motility on successive examinations of the same patient (Table II).

TABLE II.—EMPTYING TIME (MINUTES) ON DIFFERENT OCCASIONS IN THE SAME INDIVIDUALS.

Case number.	Exam. 1.	Exam. 2.	Exam. 3.	Diagnosis.
148	10	20	10	Duodenal ulcer
27	40	5	..	Duodenal ulcer
150	70	20	..	Gastric ulcer
18	10	100+	..	Duodenal ulcer

Discussion. An attempt has been made to evaluate the diagnostic information which may be obtained from studies of gastric function. The present consideration confines itself to the question of volume of gastric secretions, reaction of gastric juice and motility of the stomach, leaving aside such conclusions as may be drawn from demonstration of abnormal elements in the gastric contents (blood, pus, and so forth) or from demonstration of gross food retention (pyloric obstruction).

The results indicate that on the whole the applications of gastric analysis are of restricted value. There are, however, certain findings which seem to us very useful, both from the standpoint of positive and negative diagnostic significance, provided that determinations of volume of secretion and of pH of gastric juice are made; but it should be emphasized that no picture as revealed by gastric analysis (as defined above) is absolutely characteristic of any special disease.

Ten-minute secretion volumes of over 40 cc. immediately raise a suspicion of gastric or duodenal ulcer. If the titratable acidity in the same case is high (90 or more) this suspicion becomes almost a certainty, although there are certain exceptions. Conversely, ten-minute volumes of over 15 or 20 cc. practically rule out the presence

of cancer or extensive gastritis (pernicious anemia), especially if it can be shown that the stomach can secrete acid.

Very small volumes of gastric secretions (10 cc. or less per ten-minute period) on the other hand are practically diagnostic of serious organic disease of the stomach (cancer, and so forth), especially if there is failure to secrete acid after histamine.

Aside from these findings, there does not appear to be any correlation between the results of gastric analysis and the morbid condition. We have found no picture characteristic or even suggestive of gall stones, appendicitis, gastric neurosis and other disorders. Barring the finding of pyloric obstruction, the motility of the stomach has in our hands given no clue whatever as to diagnosis.

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NOTE.—In our paper which appeared in "The Archives of Internal Medicine," 1926, **37**, 819, the formula (1) on page 822 should be $[\frac{x}{y} \times A] - A =$ Maximum possible amount of juice secreted in a ten-minute period instead of $[\frac{y}{x} \times A] - A =$ Maximum possible amount excreted in a ten-minute period.

CHRONIC ULCER AND CARCINOMA OF THE STOMACH.

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RECENT revival of the discussion, with misquotations and false understanding, of the relationship of gastric ulcer and gastric carcinoma demands a restatement of our knowledge and a brief presentation of practical pathologic and clinical facts which serve to prevent and possibly cure many gastric carcinomas. It is also time to emphasize again the necessity of realizing the impossibility of differentiating, clinically, early gastric carcinoma from gastric ulcer, a fact which necessitates exploration and microscopic examination if we expect to prevent the fatal results of late gastric carcinoma by correct early diagnosis and treatment.

The evolution of our present knowledge of this subject has been dependent on increasing opportunities to study both lesions. These opportunities have changed from time to time in the last twenty-five or thirty years, at the beginning of which time all of our knowledge was based on observations of material found at necropsy, which

rarely, if ever, reveals the conditions as they are seen during life. Despite the latter fact, such material presented enough evidence to allow many authorities—Cruveilhier (1839), Rokitansky (1840), Dittrich (1848), Brinton (1856), Lebert (1878), Zenker (1882), Hauser (1882), Berthold (1883), Rosenheim (1888), Wetzoldt (1889), Duplant (1898), Hayem (1901), Fuetterer (1902) and others—to state that gastric ulcer and carcinoma occur in the same stomach;[6] their observations and clinical histories led them to believe there might be an etiologic and a histogenetic relationship.

Clinicians, at the beginning of the twentieth century, were practically unanimous in the opinion that carcinoma of the stomach was a hopeless disease; when the lesion was palpable upon physical examination it was inoperable; gastric surgery was then in its infancy and the immediate risk of gastric or intestinal resection was so great that few surgeons dared to endanger their reputations and surgical progress in an almost hopeless task. As operative technique improved and abdominal explorations became more frequent and more successful, some of our bolder and more skillful surgeons attempted the resection of large gastric lesions. As a result of such attempts, in the first decade of this century we saw only massive neoplasms (Fig. 1, *a*, *b*). In 1909 Wilson and I studied and reported the material resected at the Mayo Clinic and stated:

"The total amount of material studied comprised specimens from 218 cases. Eight of these were from the duodenum and were all simple ulcers. The remaining 210 were from the stomach. Of these, 47 were ulcers without suspicion of carcinoma, 2 were sarcomas, 2 adenomas and 1 a diverticulum. Of the remaining 158 cases from the stomach, 5 were ulcers with enough microscopic appearance of aberrant epithelial proliferation to place them in the doubtful class as possible transition cases. Of the remaining 153 cases which were undoubted carcinoma, 109 (71 per cent) presented sufficient gross and microscopic evidence of previous ulcer to warrant placing them in a group labeled 'carcinoma developing on preceding ulcer.' Eleven other cases (7 per cent) showed considerable evidence of precedent ulcer, but not sufficient to warrant placing them in the previous group. In 33 cases (22 per cent) there was relatively small or no pathological evidence of precedent ulcer."[9]

At the time of that report all pathologic diagnoses were made on the gross and histologic appearance. There was no such thing as detailed cytology of fresh human tissue. Pathologists were still of the opinion that the cell of carcinoma was irregular and atypical with asymmetrical mitosis, and that it arose from "cut-off" epithelium. From the material which we studied and reported, we were aware of the fact that many carcinomas occurred in the borders of lesions which possessed all of the gross characteristics of simple chronic ulcer. In that series carcinoma was the condition uppermost in our minds.

In the same year (1909) I reported my observations from a study of gastric ulcers, having found changes in the cells of the tubules which permitted the following generalizations:

"While there has been a vague feeling from the pathologic standpoint that carcinoma frequently occurs upon gastric ulcer, strong pathologic evidence has been wanting. The clinician has for years noticed that carcinoma of the stomach often follows a prolonged history of gastric ulcer, and has believed that such was the forerunner of malignancy. The evidence, however, was only circumstantial. The fact established allows and demands a stronger admonition to the diagnostician, who, as soon as he has diagnosed ulcer of the stomach, must consider the strong possibility of its becoming malignant. The chances of this occurrence may readily be seen, as stated above, in the fact that 71 per cent of our resected specimens of gastric carcinoma were associated with ulcer, and that 68 per cent of our resected gastric ulcers were associated with carcinoma. . . . The question, 'Do ulcers become malignant as one of their sequelæ?' seems, from my material, at least, to be answered in the affirmative. What percentage heal, perforate or become malignant is impossible to determine."[1]

In the report just quoted the generalizations were of a practical nature, and were made in the hope that more chronic gastric ulcers might be explored and resected with the possibility of removal of early carcinomatous lesions. As a result of this practical conclusion, smaller carcinomas have been removed and postoperative length of life of patients with gastric carcinoma has been prolonged.

In 1913 another report was made on a larger series, and at that time the following statement was made:

"Of 684 specimens which were either excised or resected from the stomach, 191 were chronic ulcers or ulcers in which no histologic evidence of carcinoma was present. There were 472 specimens which presented the characteristics of simple ulcer plus the presence of carcinoma, and 21 specimens of ulcer in which the presence of carcinoma was doubtful."[5]

In the literature numerous writers have made the mistake of computing percentages from such figures as those just quoted. If the reports are correctly read it will be seen that only the relative frequency of the two conditions in the resected material at hand is given; the figures have nothing to do with "the percentage of ulcers which become malignant." It is impossible for any one to tell how many ulcers of the stomach will become malignant, as I have repeatedly stated.

In 1913 Wilson wrote the following: "Thus, in between 60 and 70 per cent of the cases it is fair to say that there was found more or less pathologic evidence pointing to ulcer formation with scar tissue base prior to the development of proliferating epithelium in

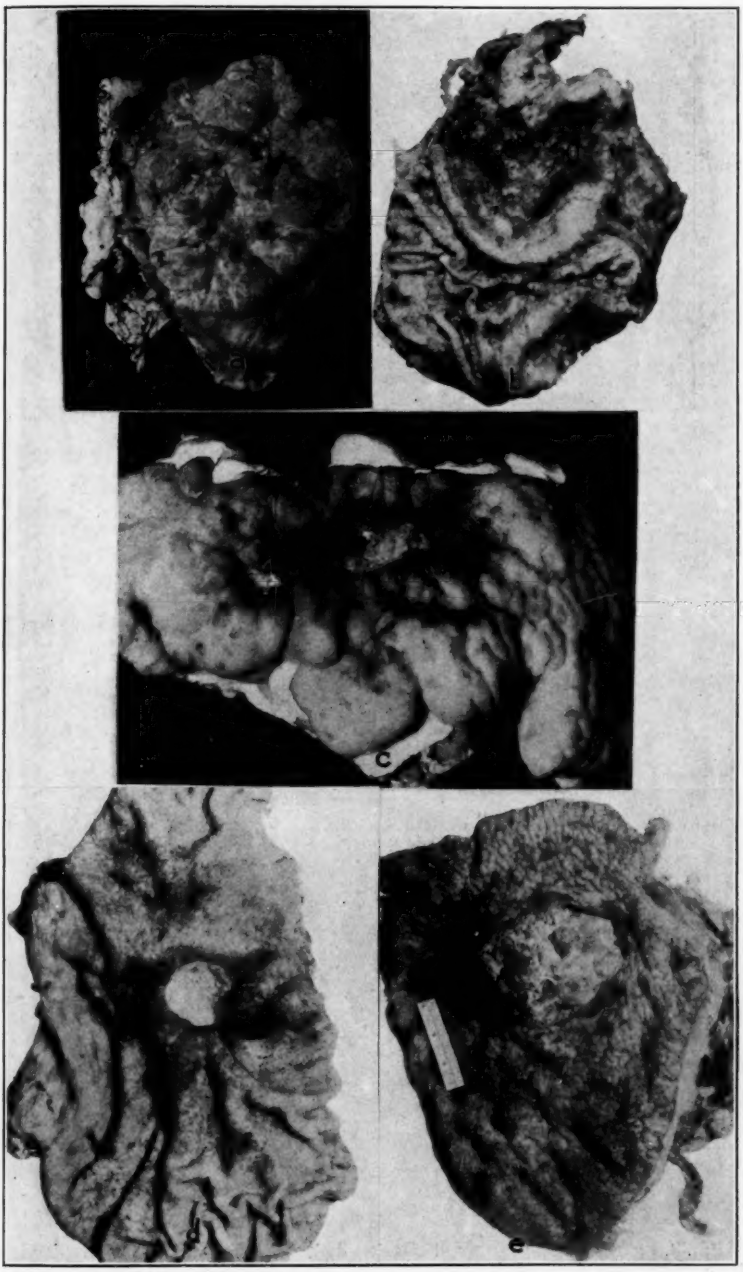

FIG. 1.—*a* and *b*, Large carcinomatous lesions. *c*, Multiple chronic gastric ulcers, the larger being carcinomatous. *d*, Chronic gastric ulcer with carcinoma in the borders, the base showing only scar tissue. *e*, Chronic gastric ulcer with carcinoma in the borders and islands of carcinoma in the base.

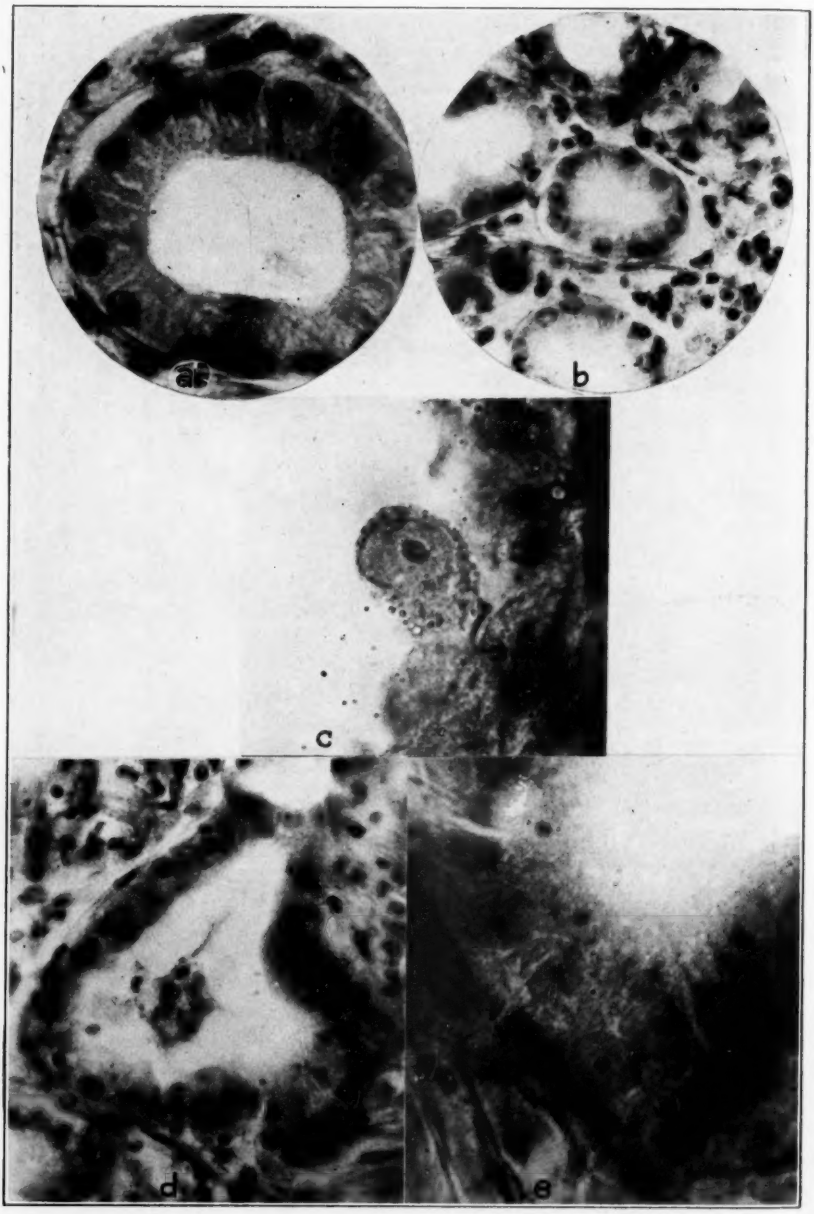

FIG. 2.—*a*, Cells lining a normal gastric tubule from the border of a chronic ulcer *b*, Gastric tubules from the border of a chronic ulcer showing changes in the structure of the cells. *c*, Unfixed cell of carcinoma. *d*, *e*, Cells frequently found in tubules of the mucosa of chronic gastric ulcers.

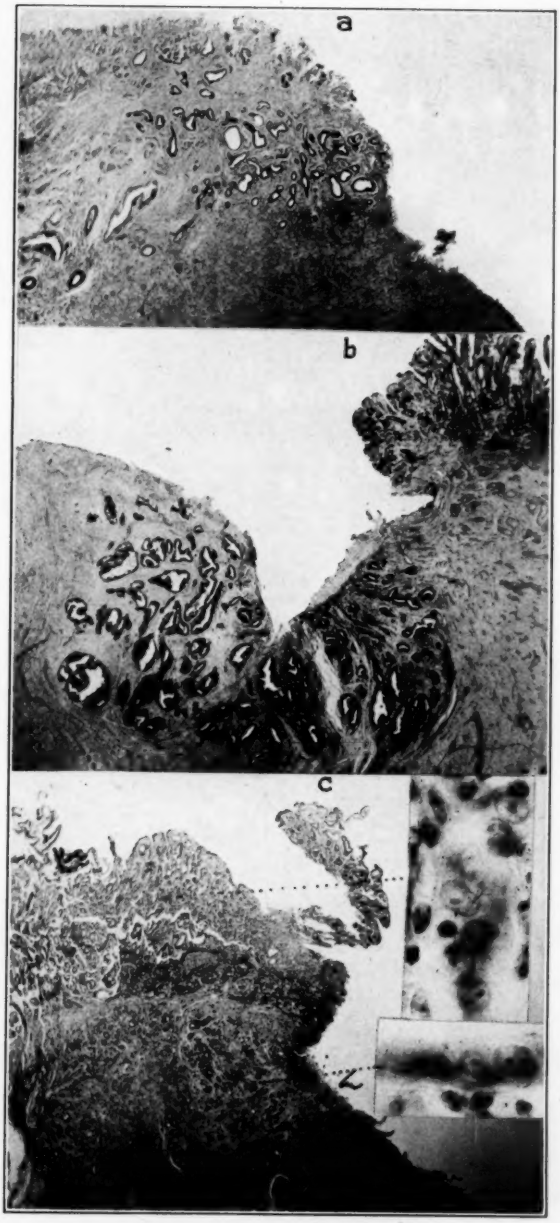

FIG. 3.—Chronic gastric ulcers.

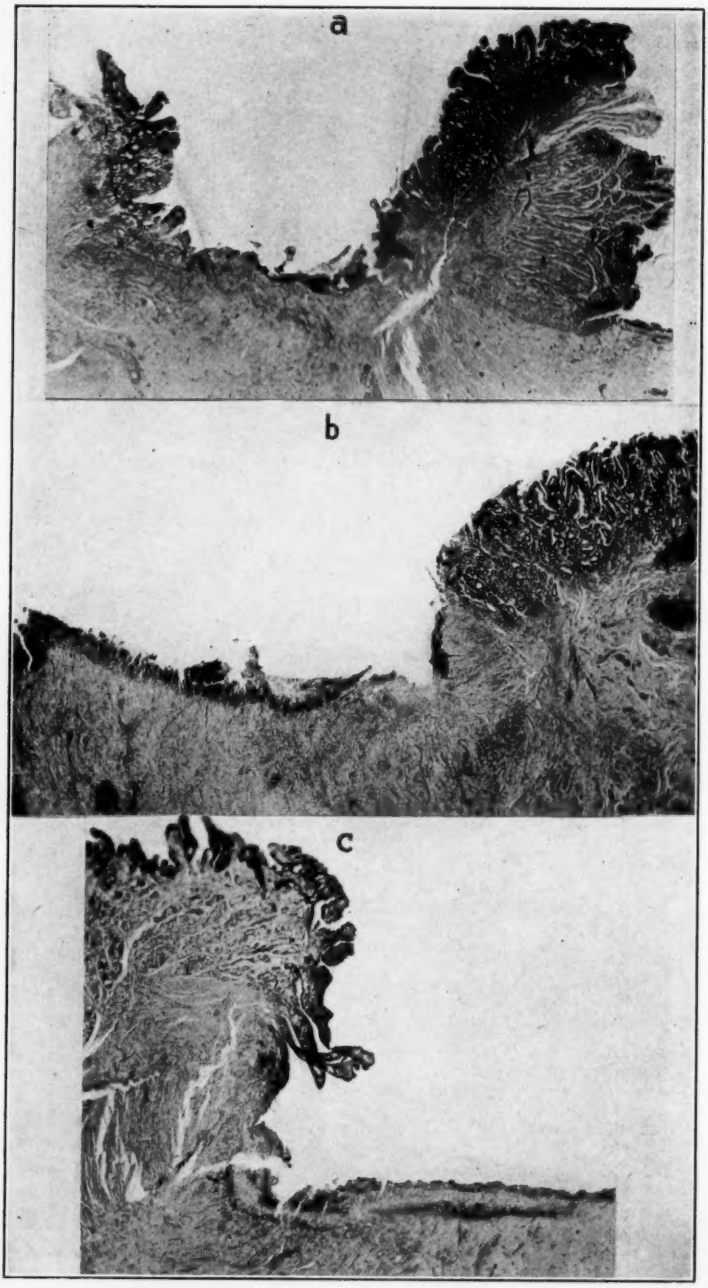

FIG. 4.—*a*, *b*, Small carcinomatous areas near the mucosa in the borders of chronic gastric ulcers. *c*, Extensive carcinoma in all of the coats of a gastric ulceration. The inserts show the character of the cells of the carcinoma and also intratubular cells of the mucosa (upper insert).

the area now occupied by the border of the ulcer, while in from 36 to 40 per cent of the cases such evidence is absent or inadequate."[7]

This means that in our carcinomatous ulcers there was the usual scar tissue in the craters, such as is seen in simple chronic ulcers. This scar tissue is of such density and arrangement that one would naturally suppose it to be of long standing; it is arranged in planes perpendicular to the surface of the crater; the carcinomatous cells invade this tissue.

Wilson also said: "It seems probable from a careful study of the clinical and pathologic evidence of this series of cases that gastric cancer rarely develops except at the site of a previous ulcerative lesion of the mucosa."[10]

In 1914 I published a report of cytologic studies of gastric tubules, and compared these findings with the cells of carcinoma. In that report it was stated that in the borders of some chronic gastric ulcers the cells in the tubules are normal in shape, being columnar and having rather small spheroidal nuclei without nucleoli (Fig. 2, *a*). Some ulcers, similar in gross appearance, may have tubules in which the columnar cells are replaced by spheroidal cells with large nucleoli (Fig. 2, *b*, *d*, *e*); these intratubular cells are frequently morphologically indistinguishable from carcinoma cells (Fig. 2, *c*). In no instance has this intratubular cytologic picture been called carcinoma, but experience has taught in a few instances that patients presenting no greater evidence of malignancy have returned with inoperable lesions after simple excision of the ulcer. This experience warrants suspicion in the presence of these cytologic changes, regardless of whether the condition is called carcinoma or not. It was this study that led Wilson to make the following statement: "Whatever may be our preconceived notions as to the relationship or lack of it between chronic gastric ulcer and gastric cancer, enough experience has now accumulated to show that we must recognize aberrant, intraglandular, epithelial proliferation as in most, if not all, cases an actual cancerous condition."[8]

In this sentence the practical clinical and economic consideration of the condition was uppermost and not an academic question of when to call a condition carcinoma and when not.

The cytologic studies already referred to have led me to make the following generalization: "Simple chronic gastric ulcers have never, in my experience, presented any visible epithelial rests which one could scientifically state were prenatal. Neither have I seen postnatal epithelial rests in the mucosa, submucosa or ulcer base that were not either composed of atrophic epithelium or real carcinoma, the latter condition being present in the base or submucosa only when there was extensive involvement of the mucosa."[2]

It may be stated that in a series of 967 chronic gastric ulcers the craters usually, if not always, contain no epithelial cells (Fig. 3).

Many writers on the subject of ulcer and carcinoma of the stomach have apparently lost sight of important practical clinical generalizations in their eagerness to learn the impossible, that is, the percentage of gastric ulcers which become malignant. This impossibility has been repeatedly emphasized by the writer:

"There are two questions which have been almost constantly asked by members of the medical profession: 'Does cancer arise in chronic gastric ulcer?' and 'What percentage of chronic gastric ulcers become malignant?' These are unquestionably interesting and important inquiries, but their practical clinical significance has been greatly overestimated; the rather vicious discussion which has taken place in medical societies and in the literature has probably done some harm. Many physicians do not differentiate the things which are of purely scientific interest from those which are of practical importance. From a purely scientific standpoint, neither one of the questions as stated can be correctly answered. No one should state positively that carcinoma arises in chronic gastric ulcer until one experimentally produces chronic gastric ulcer and produces cancer in the ulcer, and then shows that all of the conditions of the experiments are comparable to the conditions which arise in human beings."[4]

"'Does carcinoma develop in chronic gastric ulcer?' cannot be answered because there are no positive or negative facts regarding development visible in the study of simple or carcinomatous gastric ulcers. No one has experimentally produced a chronic gastric ulcer and then produced a carcinoma in that experimental ulcer. . . . 'What percentage of gastric ulcers become carcinomatous?' cannot be answered by virtue of the fact that it cannot be shown positively that carcinoma develops on ulcer."[3]

"It is important to make the diagnosis, and the differentiation of simple chronic gastric ulcer and early carcinomatous gastric ulcer cannot be made clinically. The important fact to be fully appreciated by the members of the medical profession and the laity is the common association of gastric ulcer and cancer and the present impossibility of always making a clinical differentiation."[4]

It may be seen that the writer has maintained a scientific and practical attitude toward the relation of gastric ulcer to gastric carcinoma and that what has been written has been misunderstood and misquoted. After a much larger experience (967 ulcers and 1353 carcinomas) the facts at present are:

1. Single and multiple chronic ulcerations of the stomach occur (Fig. 1, *c*).

2. In the case of multiple chronic ulcerations one may be carcinomatous, the rest being simple (Fig. 1, *c*).

3. Chronic ulcers, whether simple or carcinomatous vary greatly in size, shape and form. As a rule, most chronic gastric ulcers larger than 2.5 cm. in diameter also show carcinoma. This complication is less frequent in subacute perforating ulcers.

4. The smallest gastric carcinomas have been seen in the borders of simple chronic ulcers and not in the base (Fig. 4, *a*, *b*). Whenever carcinoma has been found in the base it has always been found in the borders (mucosa) (Fig. 4, *c*). The reverse of this is not always the case.

5. Studies of living and unfixed fresh cells of the gastric tubules in the borders of chronic gastric ulcers reveal the following significant and suggestive facts: (*a*) In some chronic ulcers the cells of the gastric tubules are columnar (perfectly normal) having small spheroidal nuclei and inconspicuous nucleoli (Fig. 5, *a*). (*b*) In others these cells are replaced by ovoidal or spheroidal cells with large nuclei and large nucleoli (Fig. 5, *b*); these cells are morphologically indistinguishable from malignant cells of gastric and other forms of carcinoma; in such ulcers the cells are all apparently intratubular there are no such cells visible in any other portion of the ulcer; at no time has this picture been called carcinoma, but it is considered suspicious, and wide removal seems the wisest and safest

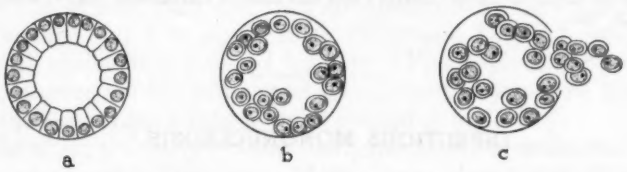

FIG. 5.—Diagrammatic representation of the cytologic variations seen in the mucosal borders of three chronic gastric ulcers: *a*, Normal. *b*, Replacement of normal epithelium by cells which have the morphology of malignant cells. *c*, The same cells invading the stroma.

procedure. (*c*) In some chronic ulcers the picture just described is found plus the presence of the cells outside of the tubules, in the submucosa, muscularis and lymphatics (Fig. 5, *c*); this picture would be called carcinoma by any competent pathologist. The preceding picture (Fig. 5, *b*), however, might well be missed by pathologists who are not cytologists and are only acquainted with postmortem or fixed and embedded tissues.

6. The relative frequency of resected carcinoma to resected or excised chronic ulcer has changed as a result of the fact that surgeons and clinicians of experience are firmly convinced of the impossibility of differentiating early carcinoma from simple gastric ulcer by any known clinical means, roentgenoscopy included. In fact, they are convinced that by clinical means other than roentgenoscopy duodenal ulcer and gastric ulcer cannot be differentiated with any degree of accuracy. Hence they resort to roentgenoscopy to determine the site of the ulcer, and if it is found in the stomach they advise exploration and excision or resection for diagnostic and therapeutic purposes.

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INFECTIOUS MONONUCLEOSIS.*

I. Report of Twelve Cases.

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The disease which is the subject of this report, and which has received from various writers the names "infectious mononucleosis," "acute benign lymphoblastosis" and "acute lymphadenosis," was first described as a clinical entity by Sprunt and Evans[1] in 1920. It is of interest chiefly because of its unusual and, at first sight, alarming blood picture; because of its invariably favorable prognosis; because it is probably of much more frequent occurrence than has been supposed. The literature prior to 1920 contains many case reports which conform exactly to the syndrome of "infectious mononucleosis;" most of these were considered by the authors as cases of acute leukemia with recovery (Cabot,[2] Hall,[3] Jackson and Smith,[4] Ludke,[5] Marchand,[6] Turck[7]). The name "infectious mononucleosis" is here applied only because it is the one which has been most widely used in referring to this condition;

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as pointed out by Schenck and Pepper,[8] if strictly interpreted it should imply that the "monocytes" or endothelial leukocytes are those chiefly concerned, whereas actually the characteristic cells are lymphocytes.

Infectious mononucleosis is strikingly a disease of young people; our 12 patients ranged from eighteen to twenty-six years of age, and the oldest patient mentioned in published reports was thirty-six years. Tidy and Daniels'[9] cases were between eight and thirteen and Major's[10] was fifteen years. Males outnumbered females 11 to 1 in our series, and in about the same ratio in other reported series. All but 2 of our male patients were university students, several being medical students, and our 1 female patient was a pupil nurse. A certain tendency to epidemicity is seen in the time of occurrence of our cases; Case I, in 1921, is the earliest case discoverable in the records of the University Hospital; no more occurred until March, 1924, when 2 cases were admitted, followed by 1 in April, 1924. There was an isolated case in November, 1924; the months of January and February, 1925, each brought 1 case, there were 3 in March, 1925, and then no more until a case was admitted in January and 1 in April, 1926. Tidy and Daniels[9] observed a definite epidemic in a school for boys. Practically all of our cases have occurred in the winter and spring months, when the incidence of upper respiratory infections in general is highest.

The onset is usually gradual, with the common prodromal symptoms of a general infection. Malaise, sore throat and either definite fever or sensations of feverishness were invariable as early symptoms in our series. Headache was complained of by 4, coryza or cough by 6, generalized aching and a "grippy feeling" by 3, chills by 2 and sweats by 1. Glandular enlargement was noticed by the patient at onset in 4 cases, preceding the sore throat by a day or two in 3 of them.

All of our patients complained of soreness of the throat. In 7 cases there was actual ulceration or exudation on the tonsils or pharyngeal wall; all but 1 of the others showed congestion of the fauces and pharynx in varying degrees, and that 1 was not seen by us during the height of the disease. In 6 of the 7 cases showing ulceration or exudation smears from the lesions were positive for the spirilla and fusiform bacilli of Vincent. Downey and McKinlay[11] state that, although some of their patients showed Vincent's organisms in their throat smears, the appearance of the throats was not that of Vincent's angina; in our cases, however, the clinical appearance and the peculiar fetid odor were certainly such as are usually considered typical of an infection with Vincent's organisms. Cultures from the throats showed the ordinary organisms, especially staphylococci and streptococci; all were negative for diphtheria.

Enlargement of the lymph nodes has been a prominent and invariable feature. It is always most marked in the anterior cervical and

submaxillary nodes, usually involving some of the posterior cervical and often the axillary, inguinal and epitrochlear nodes. In 1 case widening of the area of substernal dullness was noted, and was interpreted as evidence of enlargement of mediastinal nodes. The affected nodes vary from those barely palpable to those comparable in size to a walnut; they are firm, discrete, sometimes slightly tender but never exquisitely so. There is often, especially in the more marked cases, edema of the surrounding tissues, and slight redness of the skin. The lymphadenopathy and edema may give the neck a pyramidal contour. Sometimes only one enlarged gland is palpable in each axilla, and the epitrochlear involvement may be unilateral.

The spleen was palpably enlarged in 9 of our cases—about the same proportion as in Longcope's[12] series, and somewhat more than in most other reported series. In none of Bloedorn and Houghton's[13] 4 cases was the spleen palpable, although it is stated that in 2 the spleen was enlarged to percussion; it may be that the incidence of splenomegaly varies in different "epidemics," and possibly, too, it is to some extent proportional to the observer's expectation of finding it. The splenomegaly is never extreme, usually slight or moderate; the spleen is firm but not excessively hard, maintains its shape, and is sometimes slightly tender. We have not noted enlargement of the liver in any case; Baader[14] mentions hepatic enlargement in most of his cases, and in 1 of Longcope's[12] the liver was palpable.

The blood picture is the characteristic feature of the disease, and is usually found so on the first examination. The total leukocyte count is usually, but not invariably, increased to a moderate degree, averaging 12,000 to 15,000. Early in the disease, and during convalescence, the total number of leukocytes may be quite normal, the alteration being in the differential count. The highest total leukocyte count we have recorded was 22,400 per c.mm.; 1 of our patients had a count of 31,000 per c.mm. shortly before he came to us. The characteristic cells are lymphocytes, many of them young or lymphoblast forms, comprising from 40 to 75 per cent of all the leukocytes. The most exhaustive published study of the cytology in this disease is that of Downey;[11] he asserts that the blood picture is always readily distinguishable from that of lymphocytic leukemia by the cell morphology alone. The relative and absolute increase in the number of lymphocytes persists long after the subsidence of symptoms; most of our patients, when discharged as cured, still showed a lymphocytosis. That this lymphocytosis is not an individual peculiarity, a normal condition for those particular individuals, is evidenced by the fact that 4 of our patients when examined four to nineteen months after the disease had normal counts. Nor does this lymphocytosis seem to be an expression of an individual peculiarity in exhibiting a lymphocytic instead of

a polymorphonuclear reaction to an infection or other stimulus, for 1 of Sprunt and Evans'[1] cases, after recovery from infectious mononucleosis, had an acute follicular tonsillitis with polymorphonuclear leukocytosis; Hopmann[15] gave 1 of his patients after recovery an intramuscular injection of milk, in response to which there was the usual febrile reaction and a leukocytosis of 13,800, with 80 per cent of neutrophil polymorphonuclears.

The variation in number of cells of the granular series during the disease is less striking, but is fairly constant. Coincident with the increase of lymphocytes in the first few days of the disease, there is a decrease in the absolute number of polymorphonuclears, which may persist throughout the course. More frequently, however, the number of polymorphonuclears rises to a normal figure or slightly above normal within a few days; it may be suspected that there is an attempt at some polymorphonuclear reaction, or that this is indicative of mixed infection. The patient who exhibited the greatest increase in number of lymphocytes with a very rapid drop to a nearly normal figure exhibited also a marked coincident suppression of the polymorphonuclears, their number dropping to less than 2000 per c.mm. This circumstance is suggestive of a relationship between infectious mononucleosis and the syndrome known as agranulocytic angina.

The absence of any significant degree of anemia is striking; in 1 of our patients the erythrocyte count diminished from over 5,000,000 to 4,350,000 during the illness, but in no others was there any decrease noted. We have seen no hemorrhagic phenomena of any extent; 1 of our patients had a few petechiæ on the hard palate, and 1 gave a history of frequent epistaxis but experienced none while in the hospital. One of Downey and McKinlay's[11] patients had a diffuse hemorrhagic rash. The percentage of reticulocytes and the fragility of the erythrocytes were normal in the single instance in our series in which they were determined.

The findings on urinalysis were unimportant; slight transient albuminuria and the presence of a few casts or cylindroids were usual. In 1 case there was definite urobilinuria on three examinations. A number of miscellaneous laboratory examinations were made. Several blood cultures, some of them by the "massive" technique described by Fox and Leaman,[16] gave only such organisms as staphylococci and diphtheroids, to which no significance was attributed. Wassermann and Widal reactions, and examinations of the blood for malarial parasites were always negative.

The temperature in infectious mononucleosis is irregular, but not "septic," ranging usually in our cases from 100° F. to 103° F., reaching 104° F. in only a few instances. This irregular fever continues one or two weeks, then gradually declines to normal; occasional rises to between 99° F. and 100° F. often continue for several days after the patient is subjectively entirely well. The subjective

symptoms more or less parallel the temperature. At the height of the disease the patients are toxic, obviously very uncomfortable, and appear very ill; the throat is painful and the enlarged glands occasion considerable discomfort; coryza, cough and headache are annoying. As the onset is gradual, so is defervescence—so gradual that it is difficult to formulate a statement of the average duration of the disease; but in most cases subjective symptoms persist for two or three weeks. It is noteworthy that objective signs—lymphadenopathy, splenomegaly and lymphocytosis—persist much longer than subjective symptoms. All of our patients when discharged were subjectively entirely well and ready to resume their customary occupations; but in many instances there was at the time of discharge but little diminution in the adenopathy, the spleen was definitely palpable and the percentage of lymphocytes increased. In the 4 cases whom we have been able to follow for some months (four to nineteen) after the disease, all these abnormal features have disappeared in a few weeks. In none of our cases has the clinical condition ever been such as to give rise to fear of a fatal termination; all our patients have recovered completely without complications or sequelæ. This invariably favorable prognosis, and freedom from complications, is commented upon by almost all writers; but Tidy and Morley[17] stress the occurrence of nephritis, sometimes hemorrhagic, as a complication in some of their cases.

Acute febrile diseases with a lymphocytosis of the degree seen here are not so numerous as to give cause for the consideration of many in diagnosis. Diseases such as pertussis or Malta fever which are attended by lymphocytosis, are apt to be easily distinguishable by their characteristic clinical features. Sanders[18] reports a fatal case of Ludwig's angina with 96 per cent of "lymphocytes," but suspects that the cells may really have been nongranular myeloblasts. Weichmann[19] and Landon[20] each report a case of generalized tuberculosis with a leukemic blood picture; in the former case most of the cells were myeloblasts and myelocytes; in the latter 80 to 97 per cent were lymphocytes.

The two conditions most likely to give rise to confusion are acute lymphatic leukemia and agranulocytic angina (Schenck and Pepper[8]). In acute leukemia the total leukocyte count is usually far in excess of the 25,000 or 30,000, which appear to be about the maximum for infectious mononucleosis; leukemia is marked by anemia, purpuric manifestations and progressive deterioration; and Downey[11] is sure that a differential diagnosis can be made by the cell morphology alone. Agranulocytic angina, as described in most case reports[21,22,23,24,25] is characterized by severe ulcerative angina, extreme leukopenia with almost complete disappearance of granular cells, profound toxemia and unfavorable prognosis, and occurs chiefly in middle-aged women; those features should be sufficient for a differential diagnosis. It is the consensus of opinion in this

clinic that infectious mononucleosis is identical with the classical glandular fever of children described by Pfeiffer in 1889.[26]

The association of the spirilla and fusiform bacilli of Vincent with infectious mononucleosis is very interesting. It is frequent enough to give rise to strong suspicion, at least, of a causal relation; we have said that the organisms were found in 6 of our 12 cases, and it is described repeatedly in other case reports. The cases in which Vincent's organisms do not occur show no other difference from the case with Vincent's. We have repeatedly seen cases of Vincent's tonsillitis with only cervical adenopathy, without splenomegaly, and with a polymorphonuclear leukocytosis. We have never seen the syndrome of infectious mononucleosis associated with Vincent's gingivitis; Goadby,[27] however, in discussing acute (as opposed to chronic) Vincent's gingivitis, says: "In the absence of secondary infections the differential blood count shows polymorphonuclear leukopenia with a relative lymphocytosis." These factors suggest that there is some, as yet undiscovered, agent which is responsible for the disease, and with which Vincent's organisms are frequently associated, or that the combination of organisms is responsible. There is a growing suspicion, as yet not backed by any proof, that it may some day be demonstrated that acute lymphocytic leukemia and infectious mononucleosis are due to infection by the same or closely related organisms. While various organisms are always found in the throat lesions, they do not seem of such nature as to account for the disease. Coon and Thewlis[28] state that in a single case they isolated a diphtheroid organism from the excised tonsil and lymph node, and fulfilled Koch's postulates with the organism in guinea pigs; they give no experimental protocols, and this is the only reported instance in which culture and animal inoculation are said to have given any significant result. Whatever the causative organism may be, the indications seem clear that the portal of entry is the tonsils and lymphoid tissue of the pharynx. Thus, for the present it can only be said that the question of etiology remains unsettled.

Treatment is a simple matter, and for the most part symptomatic such as would be indicated in any mild upper respiratory tract infection. In those cases with ulcerative angina, in which Vincent's organisms predominate, we have used local applications of neoarsphenamin, 5 per cent solution in glycerin, as well as antiseptic gargles. The most effective gargles seem to be dilute hydrogen peroxid or sodium perborate solution, probably on account of their oxidizing action. In stubborn or severe cases neoarsphenamin, intravenously, seems to hasten healing of the angina. White[29] has given intravenous injections of mercurochrome-220 soluble in 1 case, and believes that recover was markedly hastened thereby.

Report of Cases. All cases were observed in the wards of the medical division of the Hospital of the University of Pennsylvania.

In the tables showing the hematology in each case the initial P represents polymorphonuclears; L, lymphocytes, including adult and immature forms; M, monocytes, including the cells formerly separately grouped as "large mononuclears" and "transitionals;" E, eosinophils; B, basophils. Attention is particularly directed to the last two columns in each table, representing the absolute numbers of granular and nongranular leukocytes, in contrast to the percentages; the absolute numbers are obtained by multiplying the total leukocyte count by the appropriate percentage figures.

CASE I.—A white male, aged eighteen years, was admitted, May 27, 1921. For seven days there had been bilateral, slightly tender, progressively increasing enlargement of the neck, with slight sore throat on sixth day. General symptoms were mild. Acute gonorrheal urethritis had been present for two weeks. He had lost 4 pounds.

Physical examination showed large and cryptic tonsils; an ulcer on the right tonsil; bilateral cervical adenopathy; a systolic apical murmur; the spleen was not palpable.

On June 7 a tonsillectomy under local anesthesia was done. One of the tonsils was examined histologically by Dr. Fox; his complete report appears in the accompanying paper.

On June 12 the patient was discharged in good condition.

The temperature was irregular for the first two days in the hospital, reaching a maximum of 102.4° F.; thereafter it was normal.

Laboratory findings included: Urine: Trace of albumin, an occasional hyalin cast and 15 to 20 leukocytes per high power field. Throat smear: Positive for Vincent's organisms. Throat culture: Long chain streptococci, micrococci and long rather broad rods; negative for diphtheria. Urethral smear: Positive for gonococci.

Roentgen ray of the chest showed the right hilum shadow large.

TABLE 1.—CASE I. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total nongranular per c.mm.
May 28, 1921 . . .	83	4.73	18,000	40	56	4	..	..	7,200	10,800
May 30, 1921 . . .	..	....	11,900	25	67	6	1	1	3,613	8,287
May 31, 1921 . . .	..	....	.....	35	56	7	1	1		
June 9, 1921 . . .	90	5.09	10,900	61	22	16	..	1	6,758	4,142

CASE II.—A white male, aged twenty-three years, was admitted, March 1, 1924. For one week he had complained of malaise, generalized aching, irregular fever, constipation and occasional nausea; throat slightly sore for three days.

The right tonsil had been removed, a tonsillar remnant on the left was slightly swollen; pharynx congested. There was bilateral enlargement of the anterior and posterior cervical, supraclavicular, epitrochlear and inguinal lymph nodes and of the left axillary. Soft systolic apical and basal cardiac murmurs were present. The spleen was palpable and somewhat tender.

Two days later the spleen was larger. By March 22, three weeks after

admission, he felt well, and his general condition was good, although he still had slight fever (99° F.), and his spleen was still palpable. He was discharged on that day.

The temperature was irregular, usually higher in the evening (101° F. to 102.6° F.) and in the morning down to 98° F. or 99° F. After two weeks it only once went higher than 99° F. to 99.4° F.

Roentgen ray of chest (March 5) was negative, except for abnormally extensive hilum shadows.

The Roentgen ray of the sinuses (March 14) showed doubtful increased density of the right maxillary.

Laboratory findings were: Blood Wassermann negative. Widal reaction negative. Blood negative for malaria on two occasions; on one specimens were taken every two hours from noon until midnight. Massive blood culture: Negative (aërobic and anaërobic). Urine: Very faint trace of albumin and a few cylindroids; three specimens showed a strong trace of urobilin.

TABLE 2.—CASE II. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non-granular per c.mm.
March 2, 1924 . .	85	4.56	6,600	63	15	20*	2	..	5,290	1,310
March 5, 1924 . .	..	....	11,100	39	21	38	2	..	4,551	6,549
March 11, 1924 . .	88	4.51	11,100	23	72	5	..	..	2,553	8,547
March 16, 1924 . .	90	4.88	9,500	31	40	27	2	..	3,135	6,365

* Throughout the series the differential counts were made by several different observers. It is probable that some of the large, immature lymphocytes were counted as monocytes—the endothelial leukocytes. There is unfortunately now no way to rectify these errors; the leukocytes are probably best classed under two headings, granular and nongranular, as represented in absolute numbers in the last two columns of the table.

Oxidase stain of blood smear: Polymorphonuclears, 35 per cent; nongranular mononuclears, mostly large, 65 per cent. Reticulated erythrocytes, 0.5 per cent; fragility of erythrocytes, begins at 0.45 per cent NaCl and is complete at 0.35 per cent NaCl.

CASE III.—A white male, aged twenty-two years, was admitted, March 25, 1924. The onset of illness was nine days previously, with headache and feverishness. On the third day there were moderate chills, temperature of 103.6° F. and sore throat; on the fourth day enlargement and slight tenderness of the cervical lymph nodes. There was continued fever between 100° F. and 102° F.

The tonsils had been removed; the pharynx was congested. All the cervical and the inguinal lymph nodes were enlarged. The spleen was palpable.

By April 4 he was symptom free, and was discharged. At present, two and a half years later, he is in excellent health.

The temperature was irregular, ranging from 99° F. to 102° F.; it was still rising to 99° F. occasionally when he was discharged.

Laboratory findings included: Urine, faint trace of albumin and a few cylindroids. Widal reaction negative. Two blood cultures, one a massive culture; each showed Staphylococcus albus hemolyticus and diphtheroids in the aërobic flasks; no growth in the anaërobic.

TABLE 3.—CASE III. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non-granular per c.mm.
March 25, 1924 . .	95	5.03	7,100	50	46	2	1	1	3,692	3,408
March 30, 1924 . .	..	....	10,800	26	68	6	..	..	2,808	7,992

CASE IV.—A white female, aged twenty years, was admitted, April 29, 1924. She had been ill for two days with sore throat, coryza, feverishness and generalized aching.

The tonsils were not large, but cryptic and greatly congested. There was slight anterior and posterior cervical lymphadenopathy, especially on the right side. The abdomen showed an old appendectomy scar; the spleen was not palpable.

On May 4 the cervical nodes were larger, and there was bilateral axillary lymphadenopathy; spleen palpable 4 cm. below the costal margin.

On May 14 the adenopathy was diminishing, the spleen was not palpable and the patient felt perfectly well. She was discharged in good condition on May 23.

The temperature was irregular, usually between 99° F. and 102° F., twice reaching 103° F.; entirely normal after the twentieth day in the hospital.

Laboratory findings were: Urine: Trace of albumin and a few hyalin casts and cylindroids. Throat culture: Negative for diphtheria.

TABLE 4.—CASE IV. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per cmm.	Total non-granular per c.mm..
May 2, 1924	89	....	10,700	26	34	40	..	2,782	7,918
May 5, 1924	..	....	22,400	19	63	18	..	4,256	18,144
May 12, 1924	..	....	18,400	12	76	12	..	2,208	16,192
May 21, 1924	..	....	10,100	38	48	14	..	3,838	6,262
December 4, 1925 . . .	80	4.4	6,850	66	29	3	2	4,658	2,192

She was seen again on December 4, 1925, about nineteen months after the acute illness here reported, and was in perfect health. She had had an ordinary attack of grippe in December, 1924, and a tonsillectomy in June, 1925.

CASE V.—A white male, aged nineteen years, was admitted, October 20, 1924. He caught "cold in his head" at a football game; sore throat, malaise, feverishness, headache, swelling of cervical lymph nodes.

He appeared acutely ill. The pharynx was congested and swollen. The tonsils were large, with white patches on both tonsils and on the pharyngeal wall behind them. The neck near the mandible was swollen bilaterally in a pyriform shape; the swollen anterior cervical nodes seemed confluent and were tender; there was edema of the periglandular tissues. Posterior cervical nodes were discrete and swollen to hickory nut size, and there was bilateral axillary, epitrochlear and inguinal lymphadenopathy. The spleen was palpable 5 cm. below the costal margin.

On October 23 it was noted that the area of mediastinal dullness was "increased" (the measurement was not recorded).

By October 30 the throat lesions had healed, under local treatment with 5 per cent neoarsphenamin in glycerin. He was discharged on November 2.

The temperature was sustained, between 101° F. and 102° F., for six days after admission, fell by lysis in the course of three days and was normal thereafter.

Laboratory findings were: Throat culture negative for diphtheria. Throat smear loaded with Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 5.—CASE V. HEMATOLOGY.

Date.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non-granular per c.mm.
October 21, 1924	....	15,500						
October 22, 1924	....	14,600	45	49	6	..	6,570	8,030
October 24, 1924	....	18,800						
October 28, 1924	....	8,600	48	47	5	..	4,128	4,472
October 31, 1924	....	9,700	51	40	5	4	5,335	4,365
March 6, 1925	4.8	7,000	52	40	6	2	3,880	3,120

He was seen again on March 6, 1925; he had been in excellent health since discharge from the hospital. His tonsils were ragged and appeared chronically infected. The peritonsillar lymph nodes were barely palpable; there was no other lymphadenopathy. The spleen was not palpable.

CASE VI.—A white male, aged nineteen years, was admitted, January 10, 1925. He had a slight "cold in the head" for two weeks, and for five days, sore throat, malaise, feverishness, profuse sweating, frontal headache.

Physical examination showed a few petechiæ on the soft palate. Tonsils were large and inflamed, with patches of whitish exudate on them. The pharynx was congested, and also with patches of exudate. All cervical lymph nodes were enlarged and tender; one node in the left axilla and both epitrochlear nodes were enlarged. The spleen was barely palpable.

He was discharged on January 16, after several days of freedom from subjective symptoms.

The temperature was between 101° F. and 103° F. for two days in the hospital; entirely normal after four days.

Laboratory findings: Throat culture negative for diphtheria. Throat smears repeatedly negative for Vincent's organisms.

TABLE 6.—CASE VI. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non-granular per c.mm.
January 11, 1925	105	5.25	14,000	40	52	8	5,600	8,400
January 16, 1925	..	.....	9,300	46	48	6	4,278	5,022
December 7, 1925	80	4.73	7,350	67	26	7	4,925	2,425

He was seen again on December 17, 1925. His tonsils had been removed in April, 1925; his health was excellent. There were barely palpable lymph nodes at the angle of the jaw on both sides.

CASE VII.—A white male, aged twenty-one years, was admitted, February 8, 1925. He had been ill for two weeks, first with diarrhea, tenesmus

and cramps; in the second week, no diarrhea, but coryza, sore throat and slight fever.

The tonsils were ragged, swollen and inflamed; the pharynx congested; the uvula edematous. All cervical lymph nodes were enlarged and very slightly tender, and there was bilateral axillary and inguinal lymphadenopathy. The spleen was not palpable.

He improved uneventfully and was discharged, symptom free, on February 15.

The temperature was irregular and often subnormal; the maximum was 99.6° F.

TABLE 7.—CASE VII. HEMATOLOGY.

Date.	Hb. %.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non-granular per c.mm.
February 9, 1925	100	10,400	49	40	11	5,096	5,304
February 13, 1925	..	12,100					

CASE VIII.—A white male, aged twenty-two years, was admitted, March 9, 1925. For four days he had had anorexia, malaise, headache, feverishness, chilly sensations, vertigo on moving about and slight soreness of the throat. "Tonsillectomy" had been done at the age of seven years.

Tonsillar remnants were present on both sides; that on the right was red and swollen, with a few white spots at mouths of crypts; that on the left small but ragged and congested. The pharynx was congested. The anterior cervical lymph nodes were bilaterally swollen, and those on the right tender; there were several enlarged nodes along the posterior borders of the sternocleidomastoid muscles. One right axillary node and the right epitrochlear were palpably enlarged. The spleen was barely palpable.

The swelling of the tonsils and lymph nodes increased, and ulceration of the right tonsil was noted; the throat was treated with 5 per cent neoarsphenamin in glycerin. On March 17 the spleen was felt 1 inch below the costal margin. He was discharged in good condition on March 25.

The temperature was irregular; maximum, 104° F.; normal after ten days in the hospital.

Laboratory findings included: Throat culture: Micrococcus catarrhalis, Staphylococcus aureus and Streptococcus mitis. Throat smear positive for Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 8.—CASE VIII. HEMATOLOGY.

Date.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non-granular per c.mm.
March 9, 1925	5.2	6,000	41	53	4	2	2,640	3,360
March 13, 1925	....	12,800	26	8	66	..	3,328	9,472
March 22, 1925	....	9,400	21	71	6	2	2,162	7,238

CASE IX.—A white male, aged twenty-three years, was admitted, March 15, 1925. A week before admission he developed painless swelling of cervical lymph nodes, without other symptoms. For four days before admission he had sore throat, feverish sensations, anorexia, malaise, headache and slight cough with little expectoration.

The tonsils were greatly swollen, with a delicate whitish membrane on

the internal surface of each. All cervical lymph nodes were enlarged, especially on the left; there were two or three enlarged left supraclavicular nodes and bilateral inguinal and left epitrochlear lymphadenopathy. The spleen was palpable.

The throat was treated with applications of 5 per cent neoarsphenamin in glycerin, and he was given one intravenous injection of neoarsphenamin, 0.6 gm. He was discharged free from symptoms on March 25.

The temperature was irregular; maximum, 102.4° F.; normal after five days in the hospital.

The laboratory findings were: Throat culture negative for diphtheria. Throat smears at first negative, later positive, for Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 9.—CASE IX. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non-granular per c.mm.
March 16, 1925	90	4.98	7,600	25	64.0	11	..	..	1,900	5,700
March 18, 1925	..	....	11,300	26*	71.5	2	0.5	..	2,994	8,306
March 22, 1925	..	....	11,300	34	62.0	4	..	..	3,842	7,458
April 4, 1925	..	....	6,650	38	55.0	4	2.0	1	2,727	3,923
December 8, 1925	90	4.64	6,100	62	31.0	5	2.0	..	3,904	2,196

* Oxidase stain.

He returned for examination about ten days after discharge; he felt well; the lymphadenopathy had receded and the spleen was not palpable. When seen again on December 8, 1925 he was still perfectly well.

CASE X.—A white male, aged twenty-six years, was admitted, March 25, 1925. Ten days previously he developed enlargement and tenderness of the cervical lymph nodes and malaise. Two days after onset a blood count was said to have shown 53 per cent of lymphocytes. He was convalescent when admitted; he had recently recovered from severe iritis, ascribed to dental infection.

The throat was negative. There was bilateral cervical, axillary and inguinal adenopathy. The spleen was barely palpable.

He was discharged on March 27.

The temperature was normal.

TABLE 10.—CASE X. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non-granular per c.mm.
March 26, 1925	100	5.2	7,200	48	43	6	3	3,672	3,528

CASE XI.—A white male, aged nineteen years, was admitted, January 27, 1926. For ten days he had had bilateral swelling of cervical lymph nodes; for two days, sore throat and feverishness.

The tonsils had been "clipped;" the surface of tonsillar remnants was covered with thick greenish yellow exudate. The pharynx was congested. There was bilateral cervical lymphadenopathy, of hickory nut size, and a soft systolic apical murmur, untransmitted. The spleen was barely palpable.

He uneventfully improved, and was discharged symptom free on February 4.

The temperature ranged between 100.4° F. and 103.2° F. for two days after admission; thereafter normal, except for occasional rises to a little over 99° F.

The laboratory findings were: Throat culture negative for diphtheria; streptococci and staphylococci predominated. Throat smear positive for Vincent's organisms.

TABLE 11.—CASE XI. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non-granular per c.mm.
January 28, 1926	90	4.69	17,000	36	57	7	6,120	10,880
February 4, 1926	..	....	5,200					

CASE XII.—A white male, aged eighteen years, was admitted, April 16, 1926. He had been subject to frequent epistaxis since childhood, much more frequent (maximum, twelve times in a week) and more profuse in the past year. Early in April he developed bilateral cervical, axillary and inguinal lymphadenopathy. For ten days he had had headache, dizziness, coryza, slight cough productive of yellowish sputum, feverishness and occasional nightsweats; for two days, sore throat; he lost 8 pounds in three months. A blood count taken April 14 (before admission) is included in the table.

The tonsils were ragged and red; the crypts contained caseous material. There was anterior and posterior cervical, supraclavicular, axillary and inguinal lymphadenopathy, bilateral; most marked in the anterior cervical group. The spleen was not palpable.

On April 22 a lymph node was removed from the neck for histologic examination; the complete report by Dr. Fox appears in the accompanying paper. He had no epistaxis while in the hospital. The slight decrease in the erythrocyte count is noteworthy. He was discharged on April 29 subjectively entirely well, but with no noticeable change in the size of the lymph nodes.

The temperature was usually between 100.4° F. and 102° F., once rising to 103.4° F.; it reached normal on the fourth day in the hospital, and thereafter occasionally rose to 99° F. or a little over.

Laboratory findings: Throat culture: Staphylococci and streptococci. Throat smear loaded with Vincent's organisms. Blood Wassermann negative. Urine: Faint trace of albumin.

TABLE 12.—CASE XII. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non-granular per c.mm.
April 14, 1926	..	....	31,000	18.0	77.5	4	0.5	..	5,735	25,265
April 17, 1926	98	5.69	21,100	22.5	72.5	3	0.5	1.5	5,170	15,930
April 18, 1926	101	5.29	19,500	29.0	66.5	4	0.5	..	5,853	13,647
April 24, 1926	..	....	8,000							
April 26, 1926	76	4.35	5,200	31.0	58.0	6	5.0	..	1,872	3,328

Platelets: 77,600 per c.mm.

TABLE 13.—COMPARISON WITH OTHER REPORTED SERIES.

Report.	No. cases.	Angina.		Vincent's +, per cent.	Splenomegaly, per cent.	Remarks.
		Congestive, per cent.	Ulcerative or exudative, per cent.			
Downey and McKinlay[11]	9	44	55	22	44	
Longcope[12]	10	60?	20	30	80	Throat condition not stated, 2, or 20 per cent.
Bloedorn and Houghton[13]	4	0?	75	75	0–50	With coryza but sore throat not mentioned, 1, or 25 per cent; "spleen not palpable but enlarged to percussion," 2, or 50 per cent.
Sprunt and Evans[1]	6	16	50	0	66	Some cases seen too late for throat lesions.
Present series	12	33	58	50	75	

Summary.—Twelve cases of infectious mononucleosis are reported; the clinical and hematologic pictures seem sufficiently distinct and definite to justify the conclusion that the condition constitutes a clinical entity.

From these cases and a review of the literature, the following are the salient features of infectious mononucleosis:

1. The usual general symptoms of an acute febrile disease of greater or less severity.
2. An increase in the lymphocytes, amounting to 40 per cent or more of the total leukocytes.
3. Lymphadenopathy.
4. Angina—either hyperemia of the fauces and pharynx, or a severe ulcerative and exudative process involving tonsils, uvula or pharyngeal wall, or all three. In the lesser grades subjective soreness may be lacking.
5. Splenomegaly.
6. The common presence of the organisms of Vincent in the ulcerative and exudative lesions.
7. Increase in the total number of leukocytes.

The prognosis is invariably favorable, and complications almost unknown.

The questions of etiology and relation to other diseases remain unsettled.

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INFECTIOUS MONONUCLEOSIS.

II. Histology of a Tonsil and a Lymph Node.

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The microscopic anatomy of the lymphatic tissue in infectious mononucleosis seems only to have been described by Sprunt and Evans[1] and by Longcope[2] and discussed briefly without illustrations. It seems desirable, therefore, to record with photomicrographs the results of study of histologic sections of a tonsil and a lymph node removed from 2 cases of this disease. There is also given a description of supravital staining, by Sabin's neutral-red-Janus-green mixture, of an emulsion made from the fresh gland. This emulsion was also stained by Wright's polychrome dye, from which preparation the cellular picture is described.

Sprunt and Evans state that the pathology is not distinctive and may suggest leukemia, lymphosarcoma or lymphadenitis. There were to be found in these cases general hyperemia and lymph cell hyperplasia. Longcope found a greater resemblance to Hodgkin's disease because of the prominence of large mononuclears. The sections of these articles dealing with the histology are given in full.

"There is nothing distinctive in the changes in the lymph glands

beyond a rather definite hyperplasia of the lymphoid cells. The sections from the 3 cases examined are quite similar, with minor variations due to the difference in the stage of the disease when the glands were excised. There is no indication of Hodgkin's disease, tuberculosis, or lymphosarcoma, and no definite histologic distinction can be made between the glands in this group and in lymphatic leukemia save in the degree of hyperplasia.

"From the left axilla the lymph node has been excised. This, on section, shows almost complete loss of normal structure. There is marked lymphoid hyperplasia of the germinal centers, the cells of which show karyorrhexic and karyokinetic nuclei. In the lymph spaces between the cords there is active proliferation of the epithelioid cells of the reticulum, with the formation occasionally of large uninuclear cells almost of giant size. A few of these large epithelioid cells are also mixed with the cells in the lymph cords. Occasionally an eosinophilic leukocyte is seen. The picture suggests very strongly Hodgkin's disease, though one would scarcely dare to make a definite and positive diagnosis.

"A cervical lymph node from Case III presented a picture which simulated in some respects Hodgkin's disease, but was not sufficiently characteristic to allow one to make that diagnosis."

The findings in our lymph gland are comparable to those just given. The tonsillar microanatomy varies and perhaps for a good reason, to wit, secondary inflammation.

CASE I.*—Tonsillectomy during mononucleosis. The organ was large and soft, with a few filled up crypts, and a small ulcer from which organisms of the Vincent type could be stained. Histologically, there was noted a very decided solidity of lymph cell growth, with here and there irregular fields of larger cells, which probably represented germ centers. The lymph cells were of the usual kind, with nuclei varying from 4 to 7 μ. The masses of large cells showed many with pyknotic, karyorrhectic and karyolytic nuclei. A few seemingly normal mitoses were found. No very large cells with more than one nucleus or resembling the lymph node reticulum cell were found. A small amount of fine pigment was found. There were no strands of large mononuclears. Phagocytosis of cells and débris by large cells was almost absent. The epithelium was retained on the edge of the section, although many mononuclear and polynuclear cells were found in its layers. In the crypts the epithelium was retained in places, degenerated in others. Two small areas of active inflammation were found near the epithelial covering.

This tonsil, therefore, revealed a marked small mononuclear hyperplasia, with acute inflammation and without prominence of large mononuclears.

* These cases correspond to the clinical citations by Dr. Cottrell in the first section of this article.

CASE XII.—Cervical lymph node removed during late active stage of mononucleosis. The node was deep pink, homogeneous and moist. The notes taken from our laboratory description are as follows:

"Tissue is distinctly recognizable as lymph node. The capsule is wide, connective tissue is hyalin; the lymph channels of the capsule are distended and contain a pink staining clot enclosing mononuclears. The veins are similar but, of course, with distinct walls. The marginal sinus is open in places and collapsed in others. Trabeculæ are not numerous and are delicate. Follicular border is present; the follicles are irregularly placed and of varying sizes. The germ centers are reasonably distinct. The central vessel is not prominent. The follicles are formed almost exclusively of quite small, normally made lymphocytes. The germ center contains the usual vesicular mononuclears. Strands and sinuses are not clearly separable. Small mononuclears are the most numerous, and indeed they probably constitute 95 per cent of the cells. The large mononuclears are of four varieties. The first is a large cell with an irregular, moderately well stained nucleus, clear nucleolus or two nucleoli; its protoplasm is lightly acidophilic. The second resembles a very large plasma cell. The third is a cell similar to the first but larger, neutrophilic in cytoplasm, phagocytic of red cells and occurs more along the sinuses—a reticuloendothelial cell. The fourth is a large vesicular cell with delicate nuclear strands and barely distinguishable cytoplasm. All these cells give the impression of being very soft, and most of them are molded to their place. Two multinucleated phagocytic cells were encountered. The nuclei in order measure: No. 1, 4 to 6 μ; No. 2, 7 to 8 μ; No. 3, 7 to 10 μ; No. 4, 8 to 9 μ. There is no pigment. There are some cells with very deeply staining, homogeneous nucleus, some with a nucleus broken, which are probably degenerating small mononuclears. Mitoses are not numerous; what is probably direct division was seen once. Phagocytosis of fragments is fairly common; here and there, what seems to be a red cell, has been taken up, but polynuclears are not enclosed. Indeed, myeloid cells are exceedingly scarce. Connective tissue is delicate and not increased. There are no necroses or tubercular nodes.

Summary. A slightly hyperplastic gland with some degeneration of the small mononuclears and very marked phagocytosis by large mononuclears. There is some separation of tissue, as if by edema.

An emulsion in saline of pH 7.4 was made by gentle dabbing of the cut surface of the gland into the fluid in a dish. A drop of this was placed on a cover glass and applied to a slide prepared by the usual method for supravital staining, using a mixture of 0.8 cc. of 0.1 per cent neutral red in 10 cc. absolute alcohol to 2 cc. of absolute alcohol, to which was added 6 drops of saturated alcoholic Janus green. The slides were incubated thirty minutes before examination and reëxamined five hours later.

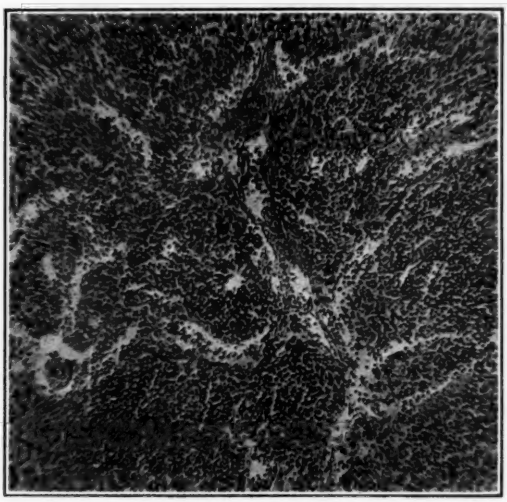

FIG. 1.—Case XII; lymph node. Low power of field near edge showing looseness of tissue and attempt at retention of architecture.

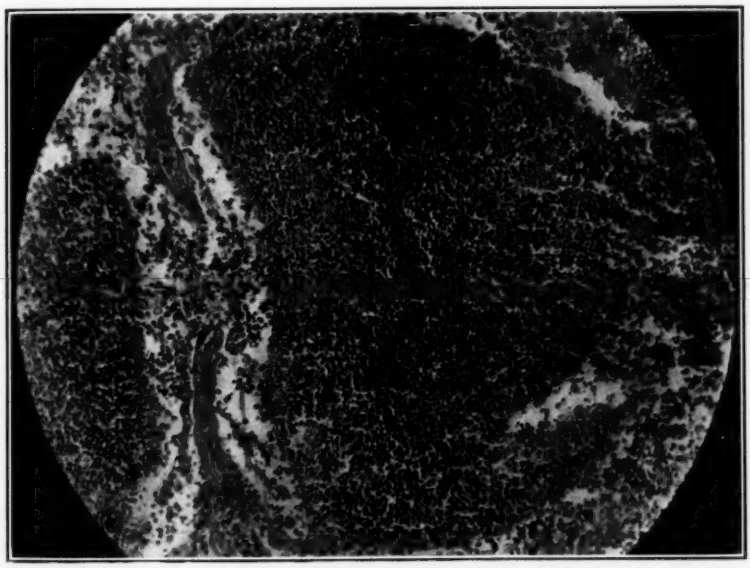

FIG. 2.—Case XII; lymph node. Follicular area with loss of normal arrangement and many loose cells in a sinus.

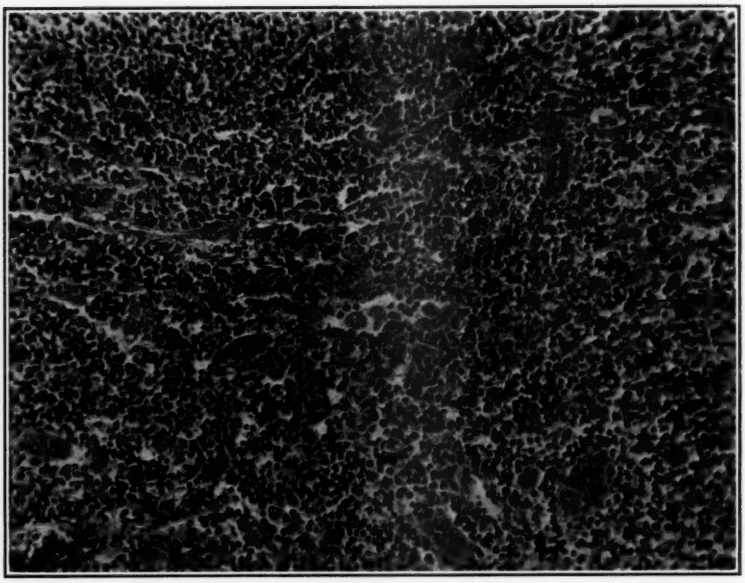

FIG. 3.—Case XII; lymph node. Closely packed cellular area with irregularly distributed large mononuclears.

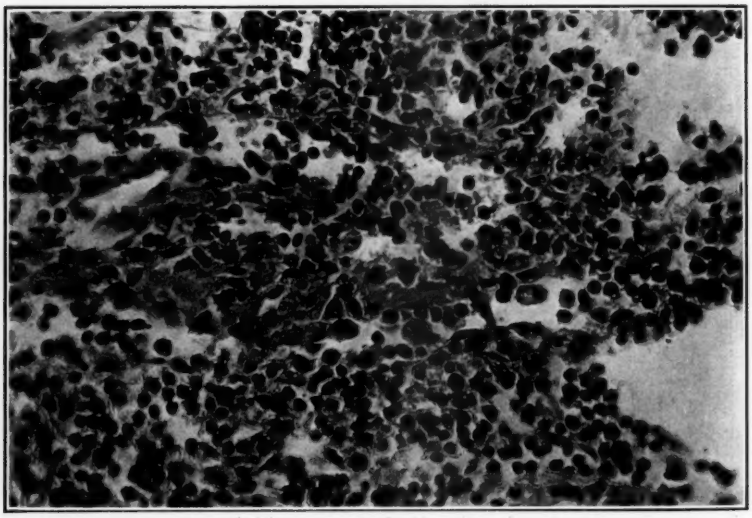

FIG. 4.—Case XII; lymph node. High power of a loose area to show relative number of large and small mononuclears.

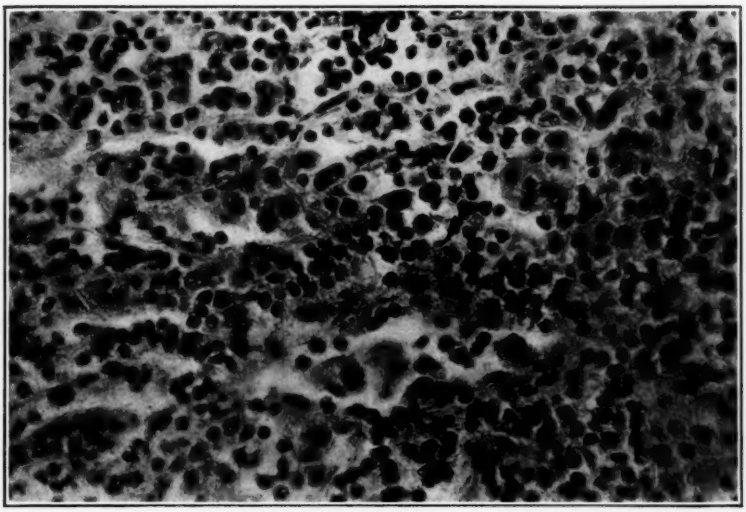

FIG. 5.—Case XII; lymph node. High power to show size, character and phagocytosis (just below middle) of large mononuclears.

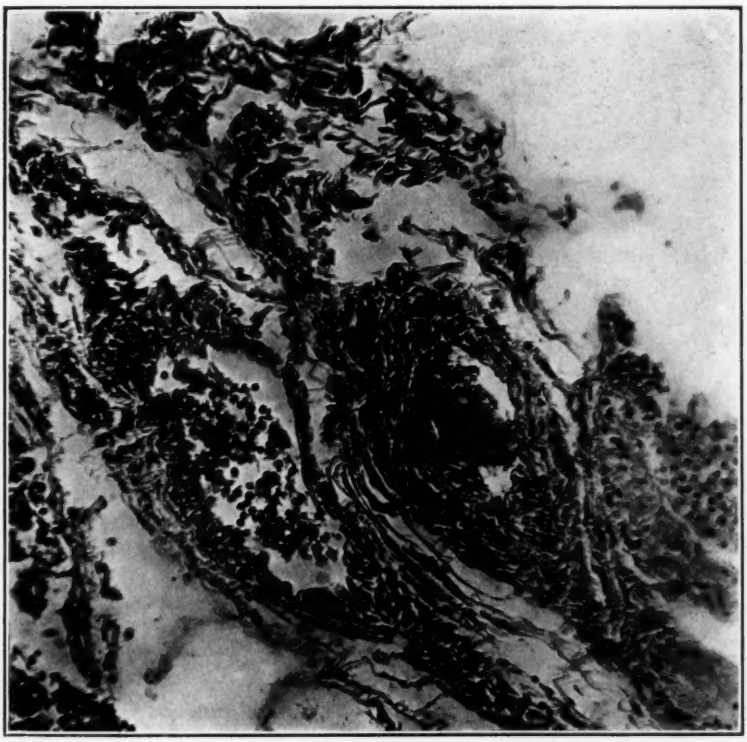

FIG. 6.—Lymph node. Dilated lymph channel in capsule of lymph node containing many small mononuclears. Vein also with recent clot.

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The variation in the staining of the smallest mononuclears was quite pronounced. The large cells seemed to be the same in all fields and in all slides. All the cells seemed soft and easily compressed when lying in groups. The elements seemed to correspond to the lymphoid series in 93 per cent of the individuals. The remainder resembled clasmatocytes, polynuclears and reticulum cells. There were no monocytes, nor serosal cells, nor could any cells be found with dispersed fine granules stained by Janus green. The larger mononuclears were not entirely identic in this preparation and the histologic section, and yet close comparisons could be made.

Smears made directly from the cut surface of the gland were stained by Wright's polychrome methylene blue and by oxidase stain. Insofar as the latter is concerned, oxidase granules were found only in the occasional polynuclear and in one cell resembling a myelocyte. In the polychrome stain the elements as described in the vital staining could be identified and in the same numbers. It is noteworthy that they measured from 1 to 3 μ larger than in the supravital staining, possibly from being flattened out. The amount of cytoplasm was relatively small in all cells. Most of it was basophilic, a character best seen in the larger mononuclears of the lymphoid type. Many nuclei were neutrophilic and a few slightly acidophilic. Some nuclei were pyknotic, some broken. It seems worthy of emphasis that the small lymphoid cells in all kinds of preparations seemed soft and degenerating, if one may judge by the staining characters.

Summary. Observations on the histology of lymphatic tissue removed during the course of infectious mononucleosis and on the staining by the supravital technique of cells from a lymph node in one case are reported.

The lymphatic tissue showed marked hyperplasia, notably of the small lymphoid cells and to a less extent of the large mononuclears. Phagocytosis of fragments, but not of whole cells, was seen. The lymphocytes appeared quite soft and degenerating. By supravital staining the cells corresponded with the lymphoid elements. No monocytes were seen.

The histology of infectious mononucleosis seems not to be very distinctive, unless it be that there is a marked hyperplasia of all elements with an attempt to retain the architecture of lymph nodes. According to our tissue, however, there should be no confusion with any chronic lymphadenopathy at the height of development of mononucleosis.

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2. Longcope: Am. J. Med. Sci., 1922, **164**, 805.

THE OCCURRENCE OF LEUKOPENIA IN HODGKIN'S DISEASE, LYMPHOGRANULOMA.

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Hodgkin's disease, lymphogranuloma, has been separated from a host of simulating clinical pictures because clinically and, more especially, pathologically it possesses definite characteristics. Aside from the manifestations of mechanical pressure and the deformities due to abnormal glandular masses, there are often constitutional signs, that is, fever, asthenia, wasting, sweating and anemia. The blood forming organs are assailed and, therefore, we search in them for pathologic alteration and for changes in the circulating blood cells. As a rule, the red blood corpuscles suffer (but there is seldom any hemolysis*); the white cells, on the other hand, may remain normal in quantity and quality or they may range from a state of pronounced leukocytosis to a severe leukopenia.

The Leukocytes in Hodgkin's Disease. During almost any or all clinical phases of this disease the white cell count may exhibit no shift or variation in number, proportion or character. Some students, however, have tried to correlate the blood findings, particularly an increase or decrease in the total number of leukocytes or a polynucleosis or a lymphocytosis, with the stage and the condition of the disease. For instance, Bunting maintains that in cases of less than one year's duration there is no leukocytosis, but there is a relative lymphocytosis,† with an increase in the transitional cells and a fall in the number of eosinophils, while in further advanced and more generalized cases he encounters an increase in the total white cell count with a polynucleosis of 75 to 90 per cent. A relative increase in the number of large mononuclear cells, not lympho-

* Perhaps, it is permissible to infer the presence of an active process of hemolysis in what appears to be a specialized picture of Hodgkin's, so-called primary splenic Hodgkin's. I refer to the clinical syndrome of a large splenic tumor, sometimes with pain over this organ, and a delicate, but unmistakable jaundice (also itching) accompanied often by asthenia or excessive sweating with leukopenia and a relative lymphocytosis (Weber). The spleen receives the brunt of the granulomatosis alteration while the lymph glands throughout the body appear to be normal or scarcely attacked. In a number of details, the picture is unlike the usual case of Hodgkin's disease.

† It may be important to determine if Hodgkin's granuloma originates as a proliferation of lymphoid cells or of the reticular cells. The escape of lymphocytes into the running blood stream might be expected if the former were true (Symmers), whereas if the disease were primarily concerned with a stimulation of endothelial cells and the cells of the reticulum, then the absence of lymphocytes in the blood stream would not be surprising (Turnbull, Ewing).

cytes, especially the transitional type (19 to 33 per cent) was emphasized by Stewart.

The literature abounds in references to cases with leukocytosis. Fraenkel and Much, Weiss, and Fabian called attention to the rise in quantity of polynuclear cells, particularly in the later stages. Lincoln published very high leukocyte counts. Over 46 per cent of the cases of Desjardins and Ford had a white cell count above 11,000. To Bunting, a significant feature was the high percentage of transitional leukocytes found at any period of the illness, interpreted by him as caused by proliferation of endothelial cells of the lymph glands. (A leukocytosis, usually present, can also be absent in high or prolonged fever, as in the so-called Murchison or Pel-Ebstein syndrome.)

Leukopenia in Hodgkin's Disease. Fabian claims there is a normal leukocyte count or leukopenia in one-fifth of all cases. This seems a rather high percentage. At Montefiore Hospital the records of the last 18 cases of Hodgkin's disease (diagnosis established at autopsy or from biopsy) revealed a leukopenia (and this only a suggestive one) in 1 instance only (Case 9833). The patient had a total white count of 5200 at one time, a polynuclear differential of 55 per cent, with some myelocytic cells, probably due to bone marrow irritation. Some of these 18 cases were exposed to Roentgen ray, not a few had fever, toxemia and intense anemia.

We have no satisfactory conception of what produces any leukopenic state. For Hodgkin's disease, however, we can attempt to correlate, if possible, the occurrence of leukopenia with demonstrable alteration in bone marrow. At a glance it will be seen in this presentation that leukopenia was encountered in some patients whose bone marrow was definitely invaded by granulomatosis tissue, and, on the other hand, in other patients when bone marrow structure remained unimpaired. No evidence is available, *pro* or *con*, as to whether the physiologic functions of bone marrow share or control the production of leukopenia or enter into its genesis whatsoever. Extreme leukopenia in Hodgkin's disease has been reported by a number of men, Gütig, Mellon, Meyer, Urchs.

A. Cases with No Demonstrable Bone Marrow Changes. CASE I.—(Reported by Mellon.) *Probable Splenic Hodgkin's Disease Associated with Leukopenia (with a Relative Polynucleosis).* Mellon considered his case primary Hodgkin's disease of the spleen. The patient was a girl, aged seventeen years. She came to the hospital for a gynecologic operation, and after a few days developed fever, severe anemia and leukopenia. Within a few weeks her spleen was removed, and she showed thereafter an immediate rise of white

blood cells to 11,500. She died shortly after splenectomy. Her blood counts in detail follow:

Date (1910).	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Polynuclears, per cent.
October 25 . . .	4,500,000	90	3,000	80.5
November 8 . . .	2,800,000	75	1,600	84.0
November 15 . . .	2,600,000	60	800	84.0
November 18 . . .	(Large spleen removed)			
November 19 . . .	2,900,000	70	11,500	84.0

Autopsy, November 19: Spleen, Hodgkin's lymphogranuloma. The liver had atrophic changes. No lymph nodes involved. Examination of bone marrow not noted.

This patient had a leukopenia before splenectomy, beginning at 3000 leukocytes and falling to 800 cells by the twenty-first day. However, there was no swing in the differential count from a polynucleosis to an agranular condition. Apparently a marked leukopenia can appear suddenly in Hodgkin's disease, albeit a rather unusual form of the disease was present here. Mellon in his article quotes the published cases of Wade and Symmers (with no complete autopsy findings) as corroboration that primary splenic Hodgkin's disease is not unknown.*

Two Cases of Widespread Hodgkin's Disease with Leukopenia (but no Agranulocytosis). Through Dr. Henry M. Feinblatt's kindness, I may cite the brief outline of 2 patients, each with extreme leukopenia (not agranular in character) during life and with well established Hodgkin's lymphogranuloma lesions at necropsy, the bone marrow showing no invasion upon careful inspection.

CASE II.—N. R., aged nineteen years, complained of abdominal distress, progressive weakness and profuse perspiration. The duration of the disease was six weeks. Gastrointestinal symptoms were marked. There was excessive perspiration afternoon and evening. Examination showed the patient to be icteric, emaciated; the chest had no evidence of tuberculosis; the liver's edge was three finger's breadth below the costal margin and the spleen was not enlarged. Fever continued between 100° F and 104° F. During observation he developed enlarged lymph nodes in the axillæ and neck. Red cell count, 3,800,000; white cell counts, 2400, 2800, 3200; polymorphonuclears, 70 per cent; hemoglobin, 70 per cent. The patient developed cellulitis of the arm and forearm and died.

CASE III.—Mr. G. was a patient, aged twenty years, complaining of gastric distress, progressive weakness and cough. He had a

* Rolleston in his Schorstein Memorial Lecture on Hodgkin's lymphogranuloma (Lancet, December 12, 1925, p. 1209) mentions briefly a case of Cornwall's, Krumbhaar's case involving spleen and bone marrow (but not lymph nodes), L'Esperance's case and 2 cases considered primary splenic Hodgkin's by Ewing, (one of Donhauser and another recorded by Kummel.)

family history of tuberculosis. The course of the disease was approximately two months. It began with nausea, vomiting and progressive weakness. Examination two weeks after the onset of the symptoms revealed a slightly icteric male with a temperature of 102° F to 103° F and a rapid pulse. Cervical nodes were enlarged, lungs negative, spleen much enlarged and liver enlarged and tender. During observation there was rapid progress of the disease, with great weakness and progressive anemia. Red cell count, 2,200,000; hemoglobin, 30 per cent; white cell counts, 1400, 1600 and 1900.

A Case of Marked Disseminated Hodgkin's Disease with Extreme Agranulocytic Leukopenia and no Generalized Bone Marrow Involvement (only the Vertebral Bone Marrow was Examined; no Permission Secured for Inspection of the Rest of the Skeleton).* CASE IV.—(No. 9145.) L. R., white, male, aged twenty-eight years, was at the New York Post-Graduate Hospital in June, 1925 and had a cervical lymph node removed, which upon section pathologically confirmed the clinical diagnosis of Hodgkin's granuloma. From July 9 to November 6 of the same year he received, at the hands of a private physician, not under the auspices of the hospital, six Roentgen ray exposures, each dose and interval of treatment as follows: July 9, 1925, July 18, August 4, August 17, October 19 and November 6. At each treatment 50 cm. skin distance, 210 K.V., 4 ma. for forty minutes, using 0.5 mm. copper and 1 mm. aluminum filter; field, 10 by 15 cm. (The lymph nodes in his neck could not be felt after the third treatment.)

On December 21, 1925, he was readmitted to the hospital, complaining that during the last six weeks he had been growing steadily and rapidly weaker, that he suffered abdominal colic and that he was very constipated. He became aware of the reappearance of his neck lymph nodes, together with fever, only two weeks before readmission.

An examination disclosed bilateral cervical lymph nodes, now very large. A semiviscid exudate came from his tonsils. He seemed slightly jaundiced. His heart was not enlarged, but over its apex there was a slight soft systolic murmur. The liver and spleen were very large, and for two days before death he had signs of bronchopneumonia in his left axilla. He had continuous fever

* In this connection we wish to cite Eugen Fraenkel (Handb. d. Spez. Path. Anat. u. Hist. 1926): "(Granulomatous) nodes identical with those encountered in the spleen are found, in some cases, in those tissues closely concerned with blood formation—the bone marrow of the long medullary bones and the vertebræ. One should not fail, therefore, to investigate large portions of the skeleton. Within the medullary cavity of the severed long bones and within the spongy areas of the vertebræ, in special cases, one may discern gray opaque nodes, varying in size and number invading the vertebræ partly or entirely, sometimes so extensively that the granuloma tissue not only surrounds the dura mater but proliferates through the intervertebral foramina and so, perhaps, severely damages the spinal cord."

throughout his five weeks at the hospital, the temperature ranging from 98° F to 103° F. Laboratory tests yielded normal blood chemistry figures, a negative Wassermann reaction and an icterus index of 6. The Roentgen ray film of the chest revealed hilum thickening. A blood culture, taken a few days before exitus, contained many colonies of anhemolytic streptococci (viridans). Of particular interest were his blood counts:

Date.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Polynuclears, per cent.	Small leukocytes, per cent.	Large leukocytes, per cent.
December 23, 1925	3,720,000	58	4,200	76	7	8
December 29, 1925	3,120,000	49	4,450	53	45	1
January 4, 1926	4,048,000	48	7,200	66	15	13
January 11, 1926	3,192,000	51	2,800	77	3	6
January 18, 1926	2,704,000	47	900	0	55	26
January 19, 1926	2,256,000	38	240	0	51	32

Date.	Mononuclear leukocytes. per cent.	Disintegrated cells.	Eosinophiles, per cent.	Transitionals, per cent.	Platelets.
December 23, 1925	0	0	0	2	
December 29, 1925	0	0	1	0	
January 4, 1926	3	0	0	3	
January 11, 1926	8	0	1	5	
January 18, 1926	11	4	0	4	
January 19, 1926	10	4	0	3	79,200

At autopsy there was a disseminated Hodgkin's process, involving cervical, bronchial and abdominal nodes, liver, spleen (unfortunately no permission could be secured for inspection of bone marrow of the long bones, but the vertebræ were examined and showed no changes in bone marrow), together with multiple hemorrhagic infarctions in the lungs containing anhemolytic streptococci. Striking was the absence of any inflammatory process about these multiple lesions in the lungs. This we may interpret as a failure on the part of the patient's tissues to react to a probable preagonal bacterial invasion.

Here then (in L. R.) extreme leukopenia came suddenly, the granular cells disappearing and the total white cells falling to 240 cells within two days. Only this remarkable blood finding directed the clinician's attention to an impending death, for otherwise, despite five weeks of protracted fever of the Pel-Ebstein type, associated with Hodgkin's disease, death was not prognosticated for some time to come. In other words, clinically, there was no reason to expect him to die as suddenly as he did. The presence of fever, of a toxemia, of an anhemolytic terminal bacteriemia, the fact that Roentgen ray therapy in large doses had been employed up to six weeks before the appearance of this blood picture, not to stress the dissemination of markedly advanced Hodgkin's lesions,

each or some or all of these features may have had a part in the production of the agranulocytic leukopenia.

B. Cases with Definite Bone Marrow Involvement. CASE V.—(Reported by Gütig.) *Generalized Hodgkin's Disease with Severe Leukopenia (Terminal Agranulocytosis), the Bone Marrow Showing Granuloma Alteration.* Gütig published the case of a girl, aged eighteen years, whose autopsy disclosed Hodgkin's disease of the cervical and retroperitoneal and peribronchial lymph nodes. There was also tuberculosis of the peribronchial lymph nodes and miliary tuberculosis of the spleen. She had necrosis of the tonsils, edema of the legs and an enlarged liver and spleen. The bone marrow had extensive granuloma changes. Her blood counts were:

Date.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Polynuclears, per cent.	Lymphocytes, per cent.	Myelocytes.
September 27	....	..	800	60.0	40.0	
October 3	1,700,000	25	850	51.0	48.0	1
October 8	....	..	1,050	70.0	30.0	
October 16	....	..	1,040	35.0	64.0	
October 24	1,200,000	20 to 25	950	45.0	55.0	
November 2	....	..	700	50.0	50.0	
November 3	1,320,000	20 to 25	680	55.5	44.5	
November 8	....	..	700	65.5	34.5	
November 14	1,940,000	20 to 25	880	55.0	45.0	
November 18	1,060,000	..	1,200	1.0	99.0	
November 19	1,000,000	..	2,000	0.0	100.0	

The total white cell count, constantly low, toward the end suddenly made a feeble attempt to rise as the granular white cells vanished from the blood stream. In this case, also, the presence of necrotic tonsils provokes the suspicion that the agranulocytic state accompanied an unappreciated clinical condition of agranulocytic angina, in which, as a rule, the red blood cells and hemoglobin suffer little, if any. Gütig's patient, however, had a marked anemia with or from Hodgkin's disease, so that the reduction in hemoglobin and red blood cells would militate against the diagnosis of a possible agranulocytic angina. Vincent's angina is not mentioned in this case.

Gütig tried to produce a postprandial leukocytosis, giving his patient food during the leukopenic state while as yet no agranulocytosis had appeared. (On November 11; see table above.) The leukocytes did not increase in number. This suggestive experiment may offer a means of gauging whether or not the white-cell-forming tissues still retain their capacity to produce additional leukocytes, as noted in the blood stream, however severe a leukopenia there may be. As is well known, from the intravenous introduction of protein or bacteria there is a sudden leukopenia. This phenomenon is interpreted as an excessive depositing of leukocytes into the capillaries of the tissues of the body, so that in the blood there is a lessened number. Obviously, a postprandial leukocytosis response

could be expected in this kind of leukopenia, while in the leukopenia associated with a severe aplastic condition leukocytes would not be plentiful in the various tissues of the body.

Gütig's report resembles a case in our own experience and has particular value for us because he published a detailed description of the bone marrow changes.

CASE VI.—*A Patient with Generalized Hodgkin's Disease Accompanied by Leukopenia, the Bone Marrow Exhibiting Extensive Granuloma Lesions.* (No. 1226.) J. T. was admitted to the New York Post-Graduate Hospital, April 19, 1926, and died, May 3, 1926. He was a vigorous and well built Polish man. Quite suddenly he felt prostrated, developing drenching sweats, abdominal colic and attacks of diarrhea. He had bilateral cervical adenitis (he knew of these enlarged glands for six weeks only), right axillary nodes, large left axillary nodes, a large liver and spleen, moderate edema and his blood was anemic, with some tendency to leukopenia. An excised lymph node was diagnosed pathologically as Hodgkin's disease.

After a four weeks' absence he was readmitted to this hospital. His symptoms were aggravated. It was apparent at once that his pallor and edema were increased and that now he had ascites and bilateral hydrothorax. Despite this fluid accumulation, he had lost body weight and he was beginning to develop pronounced signs of cardiac insufficiency. The severe anemia remained unchanged and uninfluenced. His neck and axillary lymph nodes were not large, his liver seemed smaller and the size of his big spleen unchanged. Fever developed and remained during his last days in the hospital, but no leukocytosis was noted.

A study of his blood counts demonstrated that, in addition to a marked secondary type of anemia (there being anisocytosis and moderate poikilocytosis), his leukocyte cells remained low, exhibiting a tendency toward lymphocytosis with thrombocytopenia during the early days after his readmission to the hospital. He did not rally after two blood transfusions, the anemia remaining unaffected. A week prior to his death his leukocytes tried to mount and shift toward a relative polynucleosis. The blood counts were:

Date (1926).	Platelets.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Polynuclears, per cent.	Small lymphocytes, per cent.	Large lymphocytes, per cent.
February 3	102,000	3,456,000	62	5,000	40	28	25
February 16	..	3,088,000	65	3,600	50	30	10
February 18	140,000	3,712,000	62	5,200	25	27	30
February 25	..	3,448,000	60	3,400	37	39	17
March 5	218,000	3,904,000	60	4,400	36	27	24
March 8	..	3,368,000	59	3,400	36	34	21
April 19	89,300	2,384,000	48	1,600	31	40	24
April 27	..	1,152,000	20	2,400	60	24	11
May 3	..	1,016,000	20	3,000	50	25	19

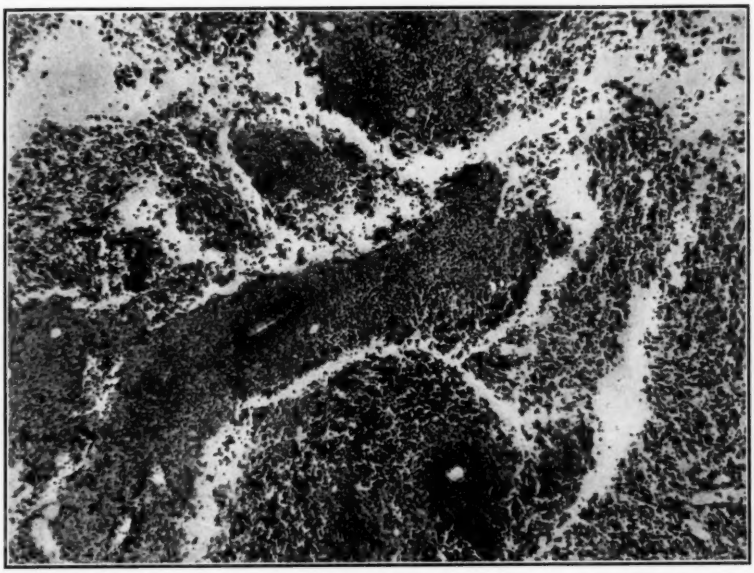

FIG. 1.

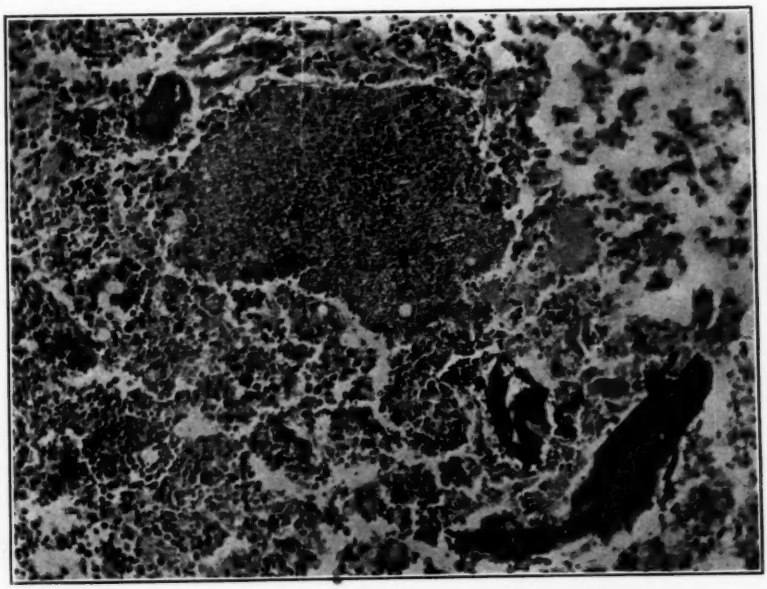

FIG. 2.

Date (1926).	Mononuclear leukocytes, per cent.	Disintegrated cells, per cent.	Eosinophiles, per cent.	Basophiles, per cent.	Transitionals, per cent.	Normoblasts, per cent.	Myelocytes, per cent.
February 3	5	..	1				
February 16	6	2	.	.	2		
February 18	3	15					
February 25	5	..	.	.	2		
March 5	10	..	.	.	3		
March 8	5	2	.	1	1		
April 19	5						
April 27	1	..	.	.	3	2	1
May 3	3	3	.	1	2	3	

J. T.'s necropsy disclosed a generalized Hodgkin's lymphogranulomatosis involving all nodes, the spleen and the bone marrow (Figs. 1 and 2). In addition there was an old tuberculous process of the peribronchial lymph nodes, an extensive ulceration of the laryngeal mucosa, a generalized edema and an early bilateral lobular pneumonia. His bone marrow, microscopically, showed a fairly good proportion of eosinophilic and neutrophilic myelocytes and leukocytes, but the marrow substance was rather poor in erythroblasts and erythrocytes and an occasional mitotic macroblast was seen. Numerous megakaryocytes and giant cells resembling the Dorothy Reed type were present. Very extensive areas of granulation tissue and of necrosis similar to those in the lymph nodes and spleen were seen. Some giant cells of the megakaryocytic type were observed, but it was difficult to decide whether they belonged to the granulomatous areas or to the elements of the bone marrow.

Discussion. Just what produces so severe a depletion of white cells in the circulating blood is not clear. For its explanation a variety of reasons has been advanced, namely, a prolonged or advanced toxemia, protracted or excessive Roentgen ray treatment, actual lymphogranulomatous infiltration replacing the erythroblastic tissue, thus causing an eventual aplasia; also arsenic therapy has been held responsible for producing bone marrow exhaustion after an initial stimulation.

Pathologically, Hodgkin's disease is an encroaching, spreading process, whereby the lymph structure (of glands, and so forth) is replaced by chronic granulomatous tissue. The lesions show, microscopically, proliferated endothelial cells, peculiar, large giant cells, eosinophilic cells, in fair numbers, overgrowing connective tissue, and clusters of lymphoid cells. These latter are, possibly, residual normal areas in lymph nodes, now almost completely invaded by granulomatous tissue; or they may represent collections of lymphoid cells gathered from the blood stream. Regardless of whether or not the pathologic process is barely visible or palpable for the clinician or clearly widespread, many authorities believe Hodgkin's granuloma always a disease of the entire lymphatic system and

blood forming organs. In most, or nearly all, cases the bone marrow is spared. However, there are instances when a depression of all the blood elements is attributable to an aplasia (nonregenerative state), paralyzing the bone marrow functionally, or else altering it to such a degree, by actual granulation tissue invasion, that the bone marrow no longer regenerates any myeloid forms. An agranulocytic white cell blood picture can, therefore appear. In Kraus-Brugsch (*Spez. Path. u. Therap. inn. Krankh.*, vol. 8) Naegeli described a case of chronic lymphatic disease, and neither in the blood nor in the histologic section of the patient's organs could he find any neutrophilic cells, indicating, to his mind, that the agranulocytosis was caused when the myeloid-cell-producing tissues were overwhelmed by the lymphatic disease.

1. *Aplasia.* An aplasia, consequently, may lead to a leukopenia, agranulocytic in type. Sometimes the blood's white cells are greatly diminished in number, and there is widespread alteration in the blood-forming tissues. For want of more precise knowledge, it is surmised that the toxin of certain diseases can do this, for example, typhoid, measles (during the incubation period), very severe pneumonias and chronic granulomatous inflammatory processes, such as tuberculosis, leprosy, syphilis, chronic glanders, actinomycosis, blastomycosis, streptothrix infections, mycosis fungoides, sporotrichosis. It is sheer speculation to assume that a leukopenia in these conditions is the result of an inhibiting or paralyzing effect of toxin upon the white blood cells in the blood stream or that the white cells are found in the blood stream in such meager numbers because toxin has directly affected the bone marrow, causing a so-called "insufficiency of the bone marrow" in a physiologic sense. (An anaphylactic leukopenia has been described, but has no particular bearing here.)

2. *Toxemia.* Whether in Hodgkin's disease we are dealing with an infection and its toxin or with a neoplastic process or, possibly, with a condition which partakes of the characteristics of infection and newgrowth is, of course, unknown. At all events it is not outside the bounds of possibility that a pronounced leukopenia in this disease may be caused by such an, as yet, undiscovered poison affecting directly the white cells in the blood stream or paralyzing the white cell response of the bone marrow. The cases cited in this text may illustrate and lend support to this conception. However, granulation-tissue invasion into the bone marrow does take place in some cases and a leukopenia present in this connection might be directly related to the bone marrow disease. Cases V and VI have bearing upon this point.

3. *Effect of Roentgen Ray.* Confusion exists as to the influence of Roentgen ray treatment in the production of leukopenia. Experimentally, Murphy and Sturm pointed out the destruction and subsequent proliferation in the germinal centers of lymph glands exposed

to Roentgen ray. They found an immediate leukopenia with pronounced lymphocytosis within a day or two after exposure and following this a gradual but well established leukocytosis by the tenth or fourteenth day. With excessive doses these workers could severely damage the germinal centers, whereupon the initial leukopenia lasted a number of days until the quickly ensuing death of the animal. For human beings we could find no clarified reports concerning the effect of Roentgen ray upon normal blood counts. The influence of Roentgen ray upon the white blood cells in diseases like leukemia is recognized, although not understood (Minot, Levin), and in the practical therapeutic use of Roentgen ray the danger of white cell depletion is assumed and guarded against (for instance, in leukemia Roentgen ray treatment is considered hazardous unless there is a concentration, at least, of 20,000 to 30,000 white cells per cubic millimeter of blood). Few cases of Hodgkin's disease escape Roentgen ray treatment nowadays, so that a leukopenia, when it occurs, may bear a significant relationship to the intensity of Roentgen ray exposure and to the interval of time between treatment. There remains the possibility of a delayed Roentgen ray effect manifesting itself as a leukopenia.*

4. *Bacteriemia.* Since a leukopenia has been noted after a sudden intravenous injection of bacteria (for example, typhoid bacilli) it might be urged that in L. R. a leukopenia followed a sudden blood stream invasion by anhemolytic streptococci. Even if there were incontrovertible proof that bacteria can cause such a leukopenia we would still have to account for the agranular character of this leukopenia in L. R.'s case, and for the absence from his tissues and organs of accumulated granular white cells which might have been swept out of his blood circulation. As a matter of fact, the dissection of this patient's organs, the lungs notably, revealed large clumps of bacteria with no surrounding zone of white cells whatsoever; evidently his tissues failed to respond to the presence of bacteria. Inasmuch as the depletion of his white cells went hand-in-hand with an aggravation of his anemia and with a striking reduction in the number of his platelets, we cannot exclude the probability that his bone marrow and blood-forming tissues suffered a severe general aplasia.

Differential Considerations. The pathogenesis, whatever it may prove to be, of Hodgkin's lymphogranuloma is, perhaps, responsible for the occurrence of a severe leukopenia. Nevertheless, as we have tried to indicate, a variety of causes, alien and unrelated to Hodgkin's disease, may produce a white cell depletion and, obviously, such a leukopenia might be discovered in any patient already afflicted with Hodgkin's disease. There remains, however, a variety of simulating conditions in respect to the leukopenia or to the

* I could not find any carefully controlled observations on this point.

absence of granular cells, and these clinical situations deserve a word of discussion.

Simple lymphocytosis can be produced by severe sepsis or poisoning from extraneous substances like benzol, or by particular infections like pertussis, or by chronic inflammatory processes as tuberculosis, leprosy, syphilis, actinomycosis, blastomycosis, mycosis fungoides, glanders, rhinoscleroma, sporotrichosis. Rarely is the total white count extremely low; moreover some granular cells, however few in number, are found in the blood. It is well to distinguish in this connection a relative from an absolute lymphocytosis. Usually a so-called lymphocytosis is, in reality, a condition wherein the neutrophilic leukocytes are greatly reduced, thereby presenting a secondary but relative increase in the percentage of lymphocytes. This type of relative lymphocytosis accompanies most of the diseases just enumerated. On the other hand, true lymphocytosis, and by this we mean an actual absolute increase in the total number of lymphocytes, is comparatively rare. It does occur in pertussis for instance, the total lymphocytic counts rising to 80,000, or even to 200,000.

Agranulocytic Angina. This term is employed to designate clinically an abrupt overwhelming picture ushered in with fever, chills and severe angina involving the Waldeyer ring (necrosis of the tonsils and the nasal mucous membrane). An occasional case develops insidiously. The condition moves swiftly and is nearly always fatal. Females more than males have thus far been reported, the age incidence ranging from twenty-two to sixty-three years. Striking, indeed, is the blood picture. The granular cells seemingly escape from the blood stream, and there results a relative lymphocytosis and an extreme leukopenia. In this condition no granular cells whatsoever may appear in the blood stream, while the red blood cells and hemoglobin remained practically undisturbed. We have then, unlike the leukopenia seen in Hodgkin's disease, severe throat angina (Vincent's organisms are often present), a quickly overwhelming clinical course associated with no anemia and with no stigmata of Hodgkin's disease. Unfortunately, as already discussed, a severe anemia is frequent in Hodgkin's disease, so that under such circumstances we cannot diagnose with certainty agranulocytic angina because, to begin with, the red blood cells and hemoglobin may not have been spared. Nor is it possible to state, at this time, whether the agranulocytosis and white cell depletion are an effect of a bacteriemia or whether they indicate a peculiar failure on the part of the host to respond to bacterial infection. This point has bearing upon the consideration of agranulocytic angina as an entity *sui generis*.

Infectious mononucleosis was first recognized by Pfeiffer, and probably represents the condition formerly called glandular fever.

Frequently it is associated with Vincent's angina. Patients become acutely ill, developing sore throat, general but superficial adenopathy, enlargement of the spleen and fever. Recovery is usual. The spleen returns to normal. The red cells and hemoglobin stay practically unchanged. There is a relative lymphocytosis, most of the lymphocytes are mature forms, but a number of immature and even abnormal lymphocytic cells are present. The agranular cells run to 70 or 80 per cent, and this preponderance might arouse a suspicion of acute leukemia. No immature granular cells are found and the total white count is at 20,000 to 30,000.

Despite the fact that we have here a preponderance of agranular cells with little change in the red corpuscles or hemoglobin, also a severe angina, this condition is scarcely to be confused with any of the leukopenias described.

Acute Leukemia. Sternberg denies the validity of such a diagnosis, maintaining that the clinical picture which resembles so-called acute leukemia is, in reality and fundamentally, an infection, peculiarly capable of rousing the blood-forming organs and tissues to simulate a clinical syndrome like leukemia. Be this as it may, leukemias with palpable or visible signs of abnormal spleen, liver, nodes, skin, mucous membrane, fundi and so forth, offer small probability for confusion, because the blood is apt to exhibit large numbers of lymphocytic and lymphoblastic cells or myelocytic and myeloblastic cells in various stages of immaturity, together with hemolysis, bleedings, change in platelet count. More especially, one might have to consider the leukopenic types of leukemia, so-called aplastic or subleukemic leukemia. Stated simply, in this type there are clinical manifestations of leukemia, but with a total white count strikingly reduced, so that the blood picture of leukemia is spread before us in a limited and greatly decreased quantity of white cells.

Thrombocytopenia. A possible though remote cause for confusion might exist here for the novice, because in this condition there is a marked reduction in the total platelet count. There are, however, bleedings, an enlarged spleen as a rule, a normal coagulation time, a prolonged bloodclot retraction period and hemolytic phenomena. But there is no leukopenia and no lymphocytosis.

Aplastic Anemia. This term is meant to indicate a depletion or exhaustion of the bone marrow and blood-forming tissues. As a consequence, the sources for blood regeneration and replacement no longer function adequately, and all blood-forming elements—red cells (hemoglobin), leukocytes and platelets are depressed in number. Practically no platelets are seen and the leukopenia is extreme.

It is obvious that since we do not understand the etiology of many of the conditions enumerated above we cannot exclude them

as causative factors in the production of the leukopenia seen in Hodgkin's disease, and this takes on additional force because we do not know how or if the lymphogranuloma process alone produces any of the blood changes observed during the course of Hodgkin's lymphogranuloma.

NOTE.—I am indebted to Dr. Paul Klemperer for the autopsy reports and the photomicrographs.

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HODGKIN'S DISEASE OF THE SKIN AND MUCOUS MEMBRANES.

WITH REPORT OF A CASE WITH UNUSUAL LESIONS.

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In 1832, Hodgkin first drew attention to the disease which now bears his name, and though recent medical literature fairly teems with reports of clinical, pathologic and bacteriologic studies of this condition, its etiology remains obscure. Proper treatment may seem to retard its onward march, improvement being noted for months, or even a few years, but real cures are questionable.

In spite of classical descriptions of the clinical aspects of Hodgkin's disease, its early diagnosis is not always easy. In the large majority of cases the symptoms are caused by either (*a*) lesions of the superficial glands, (*b*) the presence of intrathoracic lymphadenoma, or (*c*) abdominal lesions.

It is, however, possible, to find Hodgkin's disease revealing its presence by cutaneous manifestations. Kurt Ziegler,[1,2] from a review of the literature and a study of 70 cases, felt that one-fourth of all cases, at some time or other during their illness, showed evidence of skin involvement. He stated that in from 5 per cent to 12 per cent of the cases the skin symptoms preceded the general ones.

In 1917, H. N. Cole[3] studied the records of 29 cases that had been observed over a period of fifteen years at the Lakeside Hospital, Cleveland, in addition to 4 personal cases and 1 seen in consultation. Of these 34, 13 showed more or less cutaneous symptoms and lesions in connection with their generalized condition. As near as can be determined from a perusal of Cole's paper, in only one is there a possibility that the cutaneous symptoms preceded the general ones.

Ziegler has thoroughly described the usual skin lesions. Cole has again enumerated them and added to the original descriptions, giving conclusions based upon his own experience. His article contains several good illustrations. The commonest skin symptom is a pruritus. Next in frequency is a prurigo-like exanthem. Rarely does one encounter a diffuse exfoliating erythrodermia. Urticaria has been seen in many cases and Kreibisch reports a generalized eruption antedating other evidence of the disease by six months. Edematous swellings, permanent or transitory, pigmentations, spotted or diffuse, and disturbances in the nutrition of the skin are also encountered. Reddish or bluish skin tumors have been described. Cole has but 1 such case in his series. Pancoast[10] has recently reported herpes zoster in several cases of Hodgkin's disease.

Fox[4] has described a case of true Hodgkin's disease of the skin and again emphasizes the rarity of such occurrences, reviewing

the literature up to date. Fox states that the histologic differentiation between mycosis fungoides and Hodgkin's disease may be very difficult. In fact, Ziegler in 1910 made the same statement, and after a detailed study of the literature, still wondered whether mycosis fungoides was not but a special form of Hodgkin's disease. It is well known that in lymphatic leukemia, lymphoid infiltrations occur in the skin and subcutaneous tissues, though, according to Butler,[5] less than one hundred such instances have been recorded. In some of the recorded cases, these infiltrations were the first and only recognizable symptom of leukemia or pseudoleukemia.

Ulcerative lesions of the skin occur only late in the disease and are of no diagnostic importance. Lesions of the mucous membranes are most rare. Ziegler[1,2] quotes Haeckel as having observed nodules in the mucous membrane of the upper lip, and Dutoit, in the hard palate. Lesions of the mucous membranes are not even mentioned by Desjardins and Ford[6] in their statistical résumé of cases occurring at the Mayo Clinic for the five year period 1915–1920.

In Kren's[11] case, ulceration of the skin occurred. Diagnoses of sarcoma, of syphilis, of tuberculosis, and even of iodism were considered at different times, in spite of negative tissue examinations. Hodgkin's disease was disclosed by the autopsy, which also revealed ulcerations of the mouth, throat, tonsils and gastrointestinal tract.

In 1911, Ziegler[2] spoke of cases where symptoms indicated early bone involvement, and suspected that other instances had been observed, but not recognized as Hodgkin's disease. A thorough radiologic study of all patients with suspected or proven Hodgkin's disease would probably reveal a larger percentage with early bone lesions. This is well shown by the discussion following the report of a case by Pfahler and O'Boyle[7] to the Roentgen Ray Society in 1924. Once their attention was drawn to this condition, several members recalled having seen radiograms suggesting similar lesions. For the most part, bone destruction has been noted late in the disease, and I too, have seen such cases.

The blood picture in Hodgkin's disease seldom shows changes sufficiently characteristic to assist in making a diagnosis. Anemia usually occurs sooner or later with, at times, increased platelets. According to some observers, leukocytosis occurs only in the presence of fever or acute infection, counts of 60,000 having been recorded. Leukopenia is often noted. In Ziegler's[1] series, 22 had counts from 5500 to 10,000, 8 from 20,000 to 30,000, 2 over 30,000, and in 18 cases leukopenia from 5500 to 2000. Eosinophiles are often increased; in 15 of Ziegler's cases from 4 to 28 per cent, though on the other hand, they were absent in but 4 cases. The percentage varied, however, at intervals in individual cases. Neutrophiles were frequently greatly increased; rarely was the percentage more than slightly decreased, this decrease being accompanied by a relative increase in the large mononuclears. Lymphocytes usually were relatively and often absolutely decreased, very seldom slightly

increased. Ziegler finds but 1 case, Gütig's, a fatal one, where with a very severe anemia and an insufficiency of the bone marrow as in aplastic anemia, the lymphocytes rose from 22 to 50 and then 99 per cent just before death, with a white count of 2000 at the time. The red cells had been about 1,000,000, the hemoglobin 20 per cent. In 18 cases where the blood was especially studied by McAlpin,[8] no unusual counts are recorded.

The following case is reported because of the unusual lesions of the skin, preceding by many months the other manifestations of the disease. These skin lesions cleared up, but in later stages of the illness, lesions of the mucous membranes appeared, with marked destruction of tissue. At necropsy the appearance of the tissues was so unusual that until a thorough microscopic study had been completed, the pathologist doubted the correctness of the clinical diagnosis. The absence of the usual gland enlargements, the finding of adrenal glands fully the size of lemons, and suggesting tuberculosis, even though other tuberculous lesions were absent, led the pathologist to suggest my giving as cause of death "secondary anemia," contributory, "adrenal tuberculosis." The adrenal involvement had apparently not caused sufficient destruction of tissue to produce any great asthenia or hypotension at a period when this might have been recognized. Ziegler states that clinical evidence of adrenal involvement has not been noted in any case reports. Laporte[9] observed a patient with asthenia, hypotension and pigmentation of the skin, but concluded upon clinical grounds alone, in the absence of other evidence, that he was not justified in assuming adrenal lesions to explain this so-called Addison's syndrome.

Case Report. *Past History.* Mrs. B. first consulted me August 8, 1914. At that time she gave a history of having been under medical care in 1908 because of "nervousness, crying spells," and also at other times because of hemorrhoids. Before consulting me, she had been treated for several months because of "pain in the left side of neck, shooting pains in the head, general miserable feeling, light-headedness, marked nervousness, irritability, and so forth" and she was "afraid she was going to lose her mind."

I had known Mrs. B. for several years. She was a good natured, usually jolly woman, with no special worries to account for her neurosis. Though only 5 feet 6 inches tall, she weighed 192 pounds, had a rather large jaw and fairly well-separated teeth, suggesting old pituitary disease. The only signs of importance were a systolic blood pressure of 160, an aortic systolic murmur, prominent abdomen, and a slight trace of albumin in the urine.

Chloral and bromides, hydrotherapy, and proper diet brought about a general improvement with a loss of 16 pounds in one month. Nervous symptoms recurred at times, but six months later, systolic blood pressure was down to 120. In 1916, very large, irreducible hemorrhoids of 20 years' standing gave considerable trouble follow-

ing the drinking of laxative waters, eating of spicy foods, and so forth. An ointment was prescribed, containing adrenalin, cocain, belladonna and tannic acid. This was used for several years, whenever indicated, that is, especially during February, 1919, when the hemorrhoids formed a mass the size of a fist, with several areas denuded of mucous membrane. Operation was consistently refused.

In March, 1917, Mrs. B. had an acute largyngitis and slight bronchitis, in August, 1918, a slight febrile throat infection. In August, 1921, she was again nervous; the menstrual periods came at intervals of 23 to 24 instead of 26 to 28 days. Her weight was 205 pounds; blood pressure, 200 systolic, 110 diastolic. The urine was normal; the phthalein excretion was 59 per cent in the two-hour period after intramuscular injection. Corpus luteum was prescribed and the diet again regulated.

On July 6, 1923, that is, after an interval of one and a half years, Mrs. B. was asked to report for examination. Her weight was 193 pounds; blood pressure, 180 systolic, 100 diastolic; pulse rate rapid, due to nervousness. The urine was entirely negative. A complete blood count was normal.

Present Illness. On March 20, 1924, Mrs. B. reported that a week before, spots had appeared at various parts of her body. She had thought they were hives, but they did not itch. Examination showed the following: Weight 187 pounds. Of the lesions referred to, 2 were seen on the back, each the size of a nickel, raised, firm, rounded, nodular. They were of the same color as the surrounding skin, possibly a little whiter in the center. A third spot was on the right side of the neck, only much smaller than the others. The urine was normal; blood: hemoglobin 85 per cent, differential normal.

March 27, 1924. Weight 183½ pounds. One new spot was noted at the angle of the jaw. A complete examination, including blood tests, revealed no other changes. The duration of the skin lesions and the absence of itching eliminated the possibility of urticaria. A drug etiology did not seem likely, as the only ones that had been used were in the ointment (presented in 1916.) The Wassermann reaction was negative. Dr. Howard Morrow was consulted. He considered the skin lesions "a curiosity," but advised repeating the blood tests in view of a possible change to a leukemic blood picture.

April 9, 1924. For over a week, she had had occasional pain in the right elbow. Nothing was found to account for this. There were no palpable glands. The skin lesions on the back had not changed. There was a new spot, the size of a nickel, on the bridge of the nose. In spite of the full, fat abdomen, the spleen edge was just palpable at the costal margin, smooth and regular. The liver was not palpable. The urine was negative.

April 14, 1924. She felt warm and "achy." Examination: Temperature, 102.8°. Pulse, 120. Nose, throat, sinuses and lungs were apparently negative. The heart was as usual. The spleen edge was palpable. The spots were larger and more prominent.

The one on the nose was extending toward the eye; those on the back had coalesced.

Dr. Morrow still thought the lesions might be due to an early leukemia, but that mycosis fungoides had to be considered. Rolleston states that in mycosis fungoides the lymphatic glands are almost always enlarged, and the cutaneous tumors much larger than those seen in Hodgkin's disease.

In spite of medication, the patient's temperature had remained around 102 for a few days, and new skin lesions had appeared, but after nine days, fever had disappeared. Excision of a nodule had not been permitted.

May 7, 1924. Weight 174 pounds. On the anterior surface of the body, there were 4 fading lesions; on the back, 12; 1 on leg. They were flat and barely visible. The abdomen was firm. The spleen was at the costal margin. The liver was 2 inches below the costal margin. Iron and arsenic were prescribed.

May 26, 1924. She had been fine for several weeks, but on the 25th her temperature had suddenly gone to 104°. Mrs. B. looked very ill, but all skin manifestations had entirely cleared up. The lips had felt swollen and numb, but no cause for these sensations had been found.

June 5, 1924. Mrs. B. was well enough to come to the office. A thorough physical examination, including pelvis and nervous system, added nothing connected with this illness. Her complexion was pale and pasty. The spleen edge was 2 inches below the costal margin, soft and sharp. The hemorrhoidal mass was as usual, not bleeding and not infected. The blood picture was remarkable. There were no polymorphonuclear neutrophiles. There were 89 per cent lymphocytes, and 9 per cent abnormal cells, apparently myeloblasts. Myeloblasts were not seen in any previous or subsequent examinations. Fluoroscopic examination showed lung fields to be clear and there was no evidence of masses in either hilum. Posterior mediastinum was clear. Radiograms of teeth were negative.

October 25, 1924. Mrs. B. had progressed nicely for over four months and then had begun to look poorly again, temperature had risen on October 21, reaching 101°–103° at night. After that she developed a swelling and edema of the right eyelid with a definite area of infection. There were harsh breath sounds with prolonged harsh expiration over the right upper posterior part of chest. She had a dry, hacking, not paroxysmal cough. The abdomen was most of the time greatly distended and tympanitic, but at times the spleen could be felt on a level with the navel. The liver dullness seemed a bit high; the lower edge came down below the rib borders. There was a systolic murmur over the entire precordium, but the cardiac murmurs were of such long standing that an endocarditis did not seem likely. A study of the literature (here presented) had made me feel that I should have considered Hodgkin's disease as a possibility long before this date.

November 12, 1924. During the last week, lesions had appeared on the hard palate. They had broken down, ulcerated, and one of them looked like a punched out ulcer, suggestive of a luetic gumma. There was also a sloughing lesion on the opposite side, and a sloughing lesion had occurred in one of the hemorrhoids. Smears had shown organisms considered as secondary invaders. Local medication had failed to check the progress of these lesions.

November 14, 1924. Fluoroscopic examination, to my surprise, still showed no chest abnormalities, that is, glandular enlargements, such as could be expected with Hodgkin's disease. Fever had persisted. Iron and arsenic had been continued and Roentgen ray treatments instituted, the mouth lesions being exposed at weekly intervals. Some local and general improvement had followed.

December 5, 1924. Mrs. B. had now developed a diffuse eruption over the extremities, trunk and back. In some places there were areas suggesting urticarial lesions; in others the patches were elevated, white in color, and of various sizes. Pruritus was intense and resisted the remedies usual in such cases. I did not feel that the eruption had been caused by the arsenic, but believed it a part of the disease. A consultant who had seen the patient on several previous occasions and who had shared my doubts, on this date had thought an aleukemic leukemia could not be excluded, because of the mucous membrane involvement.

Mrs. B. grew gradually weaker. After ten Roentgen ray treatments, they were discontinued. The slough on the left side of the hard palate had finally come off, exposing a perforation, and thereafter fluids had often come out through the nose. A general but rapid decline had followed, and Mrs. B. died December 28, 1924, nine months after the first appearance of skin lesions.

Date.	Hemoglobin per cent.	Red blood cells in millions per c.mm.	White blood cells in thousands.	Polymorphonuclears.	Large mononuclears.	Small lymphocytes.	Eosinophils.	Myeloblasts.	Basophils.	Transitionals.	
July 6, 1923	77	4.46	11.2	73	3	24	0	0	0	0	
Mar. 20, 1924	85	....	....	72	4	23	0	0	0	1	
Mar. 27, 1924	..	....	8.4	70	4	23	0	0	0	3	
April 9, 1924	80	....	10.2	68	22	6	0	0	1	3	
May 7, 1924	64	3.65	6.0	63	5	26	1	0	1	1	Reds: marked pallor.
May 21, 1924	70	3.6	7.0	64	5	27	0	0	1	3	
May 27, 1924	70	3.75	6.2	49	14	33	0	0	0	4	Slight anisocytosis.
June 5, 1924	60	3.15	5.4	0	2	89	0	9	0	0	
Aug. 13, 1924	78	4.09	8.2	67	3	26	0	0	0	4	
Aug. 20, 1924	80	4.12	8.6	66	4	27	1	0	0	2	
Sept. 4, 1924	69	3.55	6.2	65	5	26	1	0	0	3	
Oct. 1, 1924	76	3.9	6.0	66	4	28	0	0	0	2	
Oct. 15, 1924	78	4.1	6.2	66	5	23	2	0	0	4	
Oct. 21, 1924	70	3.7	5.0	65	4	27	1	0	0	3	
Nov. 12, 1924	45	2.27	2.0	37	2	57	0	0	0	4	
Nov. 25, 1924	55	2.79	3.0	65	3	31	0	0	0	1	
Dec. 23, 1924	40	2.26	2.4	63	4	32	0	0	0	1	

Necropsy performed ten hours later by Dr. G. Y. Rusk.

ANATOMICAL DIAGNOSIS. Hodgkin's disease of spleen with extensive infiltration in liver, kidneys, both adrenals, where the process is associated with extensive necrosis. Infiltration and necrosis of lymph node near head of pancreas. Marked myeloid hyperplasia of bone marrow with lymphocytic infiltration and occurrence of cells of the "Reed" type. Ulceration and perforation of the hard palate with reaction suggesting Hodgkin's type. Superficial infiltration of epicardium. Slight chronic fibrosis of myocardium. Slight interstitial pancreatitis. Aortic atheroma. Moderate obesity.

Of especial interest were the absence of palpable superficial lymph nodes, the irregular perforation, averaging 2 cm. in diameter, in the left side of the palate; and the adrenal masses. The left kidney was normal in size; the adrenal was adherent to it. On section through the kidney and adrenal, there was a large, opaque, white, necrotic area principally occupying the adrenal, but also extending into the kidney. About this area there was an area of hyperemia. Little normal adrenal tissue was to be seen. The right adrenal was also largely occupied by a similar necrotic mass which, however, did not invade the kidney tissue as that on the left. The necrotic mass on the left measured about 5 x 3 x 3 cm., that on the right, including the adrenal, measured 5 x 6 x 3 cm. It is unfortunate that circumstances never permitted microscopic examination of the skin lesions.

Gross Description. Remains of a stout female adult appearing about fifty years of age. Superficially examined, shows skin entirely negative, and no palpable superficial lymph nodes. The left side of the hard palate shows a perforation irregular in outline averaging about 2 cm. in diameter. Hemorrhoids are present. The extremities appear negative. On making the usual median incision the body fat is abundant. The voluntary muscles appear normal. The peritoneal cavity shows no fluid and no adhesions are present except as described below. The pleural cavities appear normal. The pericardial cavity contains about 250 cc. of clear straw-colored fluid.

Heart appears slightly enlarged, especially to the right. The epicardial fat is well marked. The muscle is soft and somewhat flabby. There are a few small petechiæ on the epicardium. The right auricle is full; internally appears normal. The wall of the right ventricle shows well-marked fatty infiltration. It measures about 5 mm. thick. The left auricle is negative. The mitral orifice measures 10 cm. The valve appears normal except for moderate atheroma at its base. The aortic orifice measures 8 cm. The atheroma from the mitral valve is coextensive with that along the bases of the aortic cusps. The cusps are otherwise negative. The tricuspid orifice measures 10 cm., the valve appears normal. The

pulmonary orifice measures 8 cm., the cusps appear normal. The wall of the left ventricle measures 11 mm. The endocardium shows a few yellowish spots due to fatty alteration. The myocardium is soft, somewhat pale brownish cast, and slightly mottled as if due to fatty alteration.

The first portion of the aorta shows well-marked atheroma which extends into, and surrounds the coronary orifices.

The right lung weighs 425 grams. The pleural surface shows the usual anthracosis, but otherwise appears quite normal throughout. There is an accessory upper lobe about 4 x 6 x 2 cm. On section the middle lobe shows a slight edema. The lower lobe is markedly edematous. The larger bronchi show a slight hyperemia of the mucous membrane, but no exudate is seen. The nodes at the root of the lung show well-marked anthracosis.

The left lung weighs 340 grams. It is similar to the other lung throughout, except for moderate edema at the base.

The spleen weighs 760 grams. It measures 21 cm. in length by 9 cm. broad by 8 cm. thick. Superficially it appears coarsely mottled; areas of a deep reddish-brown intermingled with areas which appear distinctly paler. This differentiation of color extends into the tissue on section. The surface of the spleen is free from adhesions. Its anterior border is lobulated. On section, in addition to the variations in color, the tissue appears moderately firm; the Malpighian bodies cannot be definitely distinguished. The tissues do not collapse; the cut vessels appear negative. No evidence of thrombosis is seen.

Liver weighs 2060 grams. It is somewhat pale, yellowish-red in color. There is a small cyst about 3 mm. in diameter on the superior surface of the left lobe. On section the liver is irregularly dotted with many small pale yellowish areas scattered throughout the liver. There is no evidence of cirrhosis. On the under surface of the liver at the site where the adrenal lies adjacent to it, there is an area of necrosis coextensive with, and adherent to a similar necrotic mass in the adrenal as described below.

Adrenals. The left kidney is normal in size. The adrenal is adherent to it. On section through the kidney and adrenal there is a large necrotic area, firm, opaque and white, principally occupying the adrenal, but also extending into the kidney. About the necrotic area there is an area of hyperemia. Little normal adrenal tissue is to be seen. This necrotic mass is less bound to the surrounding tissues than might be expected. The right adrenal is also largely occupied by a similar necrotic mass which, however, does not invade the kidney tissue as that on the left. The necrotic mass on the left measures about 5 x 3 x 3 cm., that on the right including the adrenal measures 5 x 6 x 3 cm.

Kidneys. The kidneys are of normal size. The left is encroached upon by the granulomatous mass as noted in the previous paragraph.

About this region there is some blurring of cortex. The cortex in general is of normal thickness; somewhat pale, markings rather indistinct. No gross evidence of fibrosis. Medullary substance appears negative. The pelves are negative.

At the head of the pancreas there is an enlarged lymph node measuring about 2 x 1 x 1 cm. On section, this also shows a large firm opaque white necrotic center similar to that of the adrenal picture. A few other enlarged glands are seen in this region. The pancreas proper appears to be of normal size. It is slightly increased in density, especially toward the distal portion; appears otherwise negative.

The mesenteric lymph nodes appear normal. Those in the retroperitoneal region are generally moderately enlarged, but show no evidence of necrosis. The mucosa of the gastrointestinal tract is negative throughout.

The uterus, bladder, tubes and ovaries appear normal.

Central nervous system not examined.

Microscopic Examination. Microscopic examination of heart and epicardium shows superficially a slight infiltration with lymphocytes, a few plasma cells and undifferentiated mononuclear cells. In the myocardium there are a few foci of chronic fibrous tissue replacement of the myocardium. Lungs are negative. Stomach and the remainder of the gastrointestinal tract negative.

The mouth lesion shows normal epithelium. The subepithelial connective tissue shows an extremely extensive infiltration with lymphocytes, huge numbers of plasma cells, scattered eosinophiles and occasionally a multinucleated cell with deeply staining, compactly arranged nuclei and basophilic cytoplasm.

The spleen shows some areas of marked hyperemia and other areas in which the tissues appear much more cellular. The Malpighian bodies are small. The pulp elements generally are suffused with mononuclear cells of undifferentiated type, occasional plasma cells, and scattered large mononuclear cells with clearly staining nuclei and abundant cytoplasm, and also occasionally small polynuclear cells, at times showing a cluster of clear nuclei with relatively abundant eosinophilic cytoplasm and in other instances the nuclei more compact, more deeply staining, and the protoplasm more basic. Rarely in this group of cells a mitotic figure is seen. Among the large mononuclear cells some are seen with lobulated nuclei.

Sections of liver taken through the area adjacent to the right adrenal shows an area of necrosis surrounded by an illy-defined layer containing bloodvessels apparently in part derived from the preëxisting liver vessels. This layer also contains irregular accumulations of lymphocytes, plasma cells, some fibroblastic elements, and a number of undifferentiated mononuclear cells, but no cells which are typical of the Hodgkin's process.

Sections taken from other portions of the liver, as well as adjacent to the necrotic area show almost universally an infiltration of the portal spaces by lymphocytes and plasma cells and a varying number of large mononuclear cells with varying amounts of cytoplasm.

Sections from the left kidney show a process in the region adjacent to the necrotic adrenal analogous to that seen in the corresponding portion of the liver. The kidney sections in general also show extensive, although irregular, infiltration with lymphocytes, plasma cells and undifferentiated mononuclears analogous to that seen in the liver. The kidney parenchyma shows cloudy swelling, especially the convoluted tubules.

Sections from the adrenals show extensive necrosis, the necrotic tissue being irregularly outlined by similar reactive type of cell which extends to irregular distances in between the adrenal tissue proper. Here the infiltration often takes on a perivascular arrangement. In this region occasional polynucleated cells of the type seen in the spleen are encountered.

Sections from the pancreas show a slight interstitial fibrosis which very rarely shows an infiltration with a few scattered lymphocytes and plasma cells. The islands are irregular in size, some of them reaching relatively large volumes. They do not, however, show any abnormality.

Sections from the ovaries are negative.

Mediastinal lymph nodes show marked pigmentation. The tissues are more or less dissected apart as if by edema. The lymphocytic elements are relatively inconspicuous while the endothelial are abundant. The mesenteric and retroperitoneal lymph nodes also appear edematous and contain an irregular infiltration with mononuclear cells of the endothelial type.

Sections of the special node lying near the head of the pancreas which show necrosis in the gross, shows microscopically extensive necrosis occupying practically the whole of the gland except for a superficial area where the tissues are markedly edematous, show a layer of fibrin and beyond this scattered lymphocytes, plasma cells and mononuclear cells of medium size.

Sections from the aorta show a well-marked atheroma.

Femoral bone marrow appears markedly cellular. There are small focal groups of erythroblastic elements and numerous myelocytes which predominate the picture. Most of these are apparently of the neutrophilic type, the eosinophiles being relatively infrequent. Scattered among the myelocytes are a moderate number of lymphocytes. There also occur scattered cells with large oval and single, or lobulated nuclei; the nuclei sometimes stain palely and there is abundant and moderately eosinophilic cytoplasm. These cells, while infrequent, suggest the "Reed" type of cell.

Conclusions. 1. The early diagnosis of Hodgkin's disease is not always easy.

2. Cutaneous manifestations may give the first warning of the onset of this fatal disease.

3. They may precede all other symptoms or signs by several months, and as in the present case may disappear, recur, and disappear again.

4. Lesions of the mucous membranes and of the bones are by no means so rare as the older literature would indicate.

5. A differential diagnosis cannot always be made upon purely clinical grounds, even late in the disease.

6. Very sudden changes may occur in the blood picture. Frequent examinations are necessary so as not to overlook them.

7. Considerable adrenal involvement may occur without producing symptoms leading to its recognition.

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RENAL GLYCOSURIA AND PENTOSURIA.

A Discussion of the Similarity of the Two Conditions.

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and

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(Read before Section on Medicine, College of Physicians, Philadelphia, March 28, 1927.)

The terms "renal diabetes" and "renal glycosuria" are given to a condition which is characterized by the presence of dextrose in the urine more or less continuously; by a normal blood sugar content; by the absence of the usual symptoms of diabetes; by the fact that the condition does not become true diabetes; that it sometimes

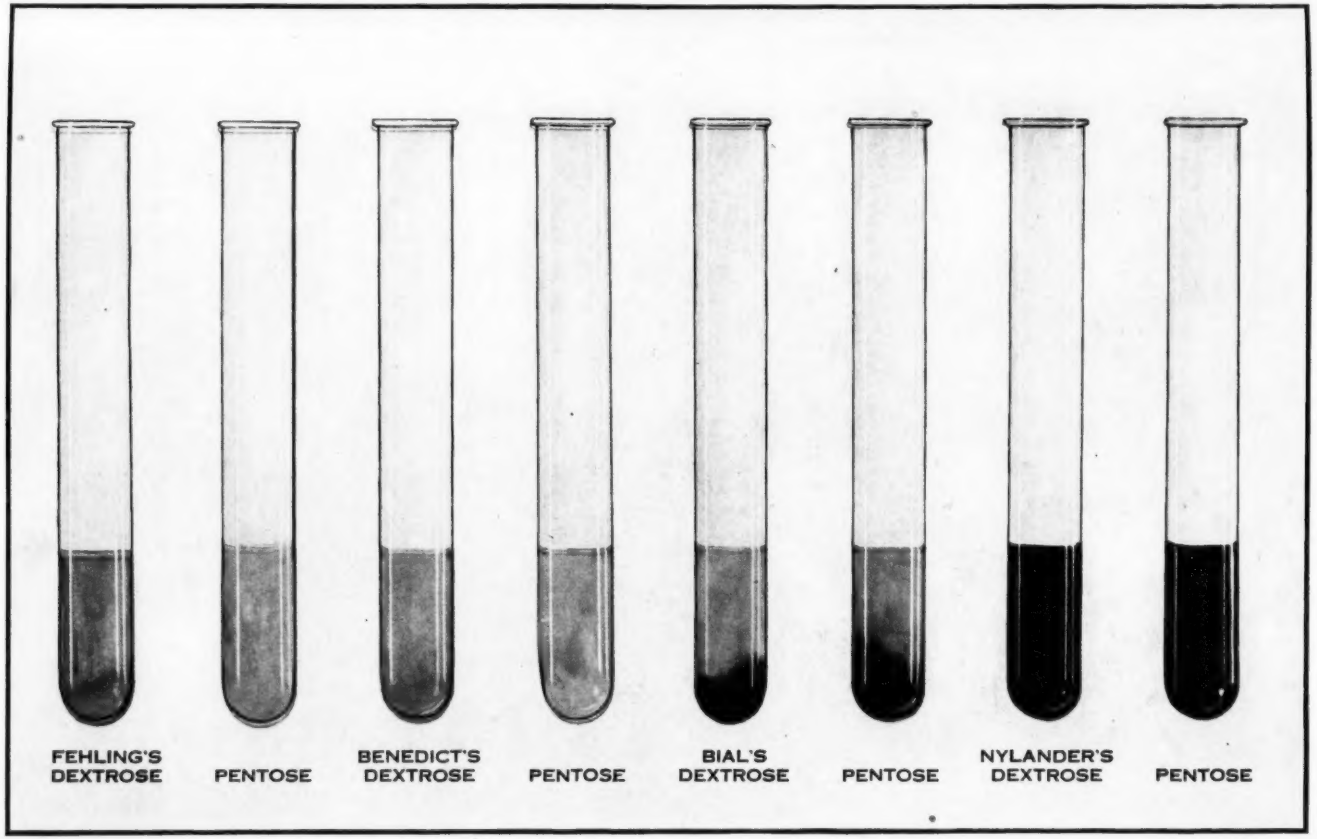
occurs in more than one member of a family; that the usual tests for renal function yield normal results; that the urine does not indicate the presence of nephritis and that the pancreatic function is not disturbed. Although the etiology is unknown, it is suggested that a congenital renal defect exists which permits sugar to be present in the urine in amounts detectable by the usual laboratory tests. Renal glycosuria is a better term for this condition than renal diabetes.

Renal Glycosuria and Diabetes Mellitus. Many cases have been reported in the literature since 1896, and the importance of the differential diagnosis between true diabetes and renal glycosuria has been emphasized. In differentiating renal glycosuria from diabetes mellitus a consideration of the following points is important: The absence of the symptoms of true diabetes; the normal blood sugar; the normal reaction of blood sugar to the ingestion of glucose and the presence of a normal respiratory quotient after carbohydrate ingestion.[3]

Essential Pentosuria. Essential pentosuria is a condition occurring most commonly in the Jewish race. It is often present in several members of the same family. It is characterized by the presence of a pentose in the urine more or less continuously; by the presence of a normal blood sugar; by the absence of evidence of deficient renal function or other signs of nephritis; by the absence of symptoms of diabetes; by the fact that a high carbohydrate intake does not increase the pentose; that the pancreatic function is normal and that the condition never becomes diabetes to the exclusion of pentosuria. Although there are less than 100 cases in the literature, pentosuria occurs more frequently than is suspected, and often goes unrecognized. Stokey,[10] in a study of routine urines, found 15 in which pentose was present. Janeway[3] stated that the condition was probably an anomaly of the intermediate metabolism and analogous rather to cystinuria and alkaptonuria than to diabetes. Characteristic symptoms are absent, although signs of unstable vasomotor control, gastrointestinal disorders and neurasthenia have been observed in many of the patients.

The similarity between pentosuria and renal glycosuria is marked. The cause is unknown. Neither present symptoms of diabetes. The blood sugar is normal. The glucose tolerance test yields similar results. The condition may be present in more than one member of a family. The renal function tests yield normal results and the urinary reducing substance reacts with Fehling's, Nylander's and Benedict's tests in such a manner that it is impossible to differentiate by this means.[5, 7]

Differential Diagnosis. The fermentation test is considered by many to be the best test to differentiate dextrose from substances which reduce the chemical test solutions, but Voit[5] has shown that under certain conditions a small quantity of *l* arabinose added to a urine from a diabetic may be fermented with the dextrose, and



The Similarity of the Reaction of Dextrose and Pentose in the Usual Reduction Test Solutions.

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Castellani,[3] in a recent article, has emphasized the fallacies of the ordinary fermentation test. (2) Bials'[1] modification of the orcein test yields a greenish precipitate and a greenish supernatant fluid with pentose. The reagent is prepared as follows: One gram of orcin is dissolved in 500 cc. of hydrochloric acid of a specific gravity of 1.151. To this add 25 drops of a 10 per cent solution of ferric chloride. Keep in an amber colored bottle. Garrod states that with this reagent a clear cut differentiation from dextrose may be obtained, but we have found that dextrose will sometimes give a precipitate very much like that of pentose. (3) The urine of most pentosurics is optically inactive, but a few apparently yield a dextrorotary osazone.[5] (4) With the phenylhydrazin test a crystalline osazone is obtained which, however, is rather difficult to differentiate from glucosazone. (5) The melting point of crystals after recrystalization serves as one of the most certain methods of differentiation.[4] The melting point of the glucosazone is 205° C. and that of the pentosazone 156° to 160° C. The theoretical nitrogen content of pentosazone is 17.07 per cent. This estimation insures complete certainty of the nature of the crystal. (6) A. Neuman[9] devised a modification of the orcein test which produces distinctive colors and spectra with pentose and dextrose. (7) Castellani and Taylor[2] were able to diagnose a case of pentosuria, using the specific bacteria by which that substance in the urine may be fermented.

Because of the similarity between these two conditions clinically, and because of the similarity of the reduction with the usual tests for urinary sugar, we investigated 52 reports on this condition found in various journals during the past seven years, with a view to determining how the diagnosis of dextrosuria was made, and whether the diagnosis of pentosuria was considered. If desired, the list of articles and tests may be obtained from the authors.

In the articles reviewed we have counted fifty tests used, but failed to find mention of the determination of the melting point of the osazone crystals or of the estimation of nitrogen content, or the Bial chemical test for pentose. The phenylhydrazin and the fermentation tests were performed in only a few instances.

Discussion. It is not our intended purpose to discredit in any way the work that has been done, but to emphasize the importance of more careful differentiation, first between dextrose and other sugars and secondly between dextrose and pentose. Renal glycosuria and essential pentosuria have much in common clinically. Differentiation with the ordinary reduction tests is impossible. In view of the results of this investigation, it may be assumed that some of the cases reported as renal glycosuria may have been essential pentosuria. We recommend, therefore, that in order to differentiate between renal dextrosuria and diabetic dextrosuria, the following tests be used: (1) The fermentation test following the suggestion of Castellani and Taylor; (2) the estimation of the respi-

ratory quotient in the determination of carbohydrate utilization; (3) the blood sugar tolerance test.

To differentiate between dextrose and pentose, the following tests should be used: (1) The Bial test, being careful to follow the technique herein described as recommended by Bial; (2) the phenylhydrazin test for dextrosazone and pentosazone crystals; (3) after recrystalization determine the melting point of the crystals; (4) the determination of the nitrogen content of the crystals; (5) the spectrum test of Neuman.

Renal diabetes might well be classed as one of the inborn errors of metabolism together with pentosuria, alkaptonuria, cystinuria and hematoporphyria congenita.

Summary. Renal glycosuria and essential pentosuria, clinically, present similar features.

Pentose and dextrose cannot be differentiated by the use of the usual reduction tests, Fehling's, Benedict's or Nylander's.

The bakers' yeast fermentation test may fail to differentiate these two substances.

Bial's test is useful, but not always accurate in the differentiation.

The differential diagnosis is made by Bial's test; by the special fermentation method of Castellani and Taylor; by the estimation of the melting point of crystals, using the phenylhydrazin test; by Neuman's spectroscopic method and by the estimation of the nitrogen content of the crystals.

The differential diagnosis between renal glycosuria and diabetes mellitus is made by the blood sugar estimation; by the blood sugar tolerance test; by the estimation of the respiratory quotient after carbohydrate ingestion.

From a survey of the literature of renal glycosuria it is noted that the phenylhydrazin and fermentation tests were performed in only a few instances, also that Bial's test, the determination of the melting point of crystals, the estimation of the nitrogen content of crystals and the special fermentation test were not used.

The possibility that some of these reported cases may have been pentosuria is suggested.

The necessity of a more careful differentiation is emphasized.

Renal diabetes might be included in the group of conditions designated as "inborn errors of metabolism," pentosuria, cystinuria alkaptonuria and hematoporphyria congenita.

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PERITONEAL ABSORPTION: COMPARISON BETWEEN THE NORMAL AND THE INFLAMED PERITONEUM.*

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Introduction. The possible difference that might exist between the rate of absorption in the normal peritoneum and that in the inflamed peritoneum was investigated with the hope that data might be obtained which would be of value in the treatment and care of clinical peritonitis.

The literature on peritonitis and peritoneal absorption is so voluminous that only a brief review will be attempted here. Carson has sketched the history of peritonitis, and Klein and McGuire have compiled bibliographies on the experimental work of more recent years in this field. Attention is called to certain historical facts as given by Carson.

In the Fourteenth Century a condition strikingly similar in its characteristics to peritonitis and known as the "iliac passion" was described. In the Seventeenth Century Thomas Willis described puerperal fever, and in the Eighteenth Century Heister reported the first case of abscess of the appendix. A great deal of attention was given to puerperal fever in the Nineteenth Century, and John Hunter pointed out that males were sometimes affected with a similar syndrome. Bichat and Laennec insisted that peritonitis was an entity. Then came the work of Pasteur and Lister, which marked the beginning of a scientific conception of the cause of peritonitis. In 1867 Koeberle, an Alsatian surgeon, first described peritonitis following abdominal operations. Vast strides were made in bacteriology in the latter part of the Nineteenth Century and for the first time peritonitis began to be studied experimentally in animals.

Certain investigations have been of particular importance in determining present conceptions of the mechanism of peritoneal absorption and peritonitis. Buxton and Torrey, Cunningham, Durham, Dutrey, Thiele and Embleton and others reported the absorption of solid particles from the peritoneal cavity into the omentum. Buxton and Torrey, Cunningham, Durham, MacCallum, Muscatello and others found absorption from the peritoneal cavity through the lymphatics of the diaphragm into the anterior mediastinal lymph nodes. Costain, Thiele and Embleton and others reported absorption from the peritoneum into the thoracic duct. Bolton, Clark, Dandy and Rowntree, Hamburger, Orlow, Putnam, Starling and Tubby, and others found that materials were absorbed

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from the peritoneal cavity directly into the blood stream through the subperitoneal capillaries.

Starling and Tubby found that dyes injected intraperitoneally appeared in the blood before the lymph of the thoracic duct was colored. Dandy and Rowntree found phenolsulphonephthalein in the urine of animals in four to six minutes after intraperitoneal injection. Oppenheimer found that toxins injected intraperitoneally appeared in the urine within fifteen minutes and that the time was not changed by tying the thoracic duct. Orlow found that after sodium chlorid solution had been injected intraperitoneally there was no increase in lymph flow from the thoracic duct. Hamburger demonstrated that there was no impairment of peritoneal absorption after ligation of the thoracic duct, and Fisher, that solution injected intraperitoneally exhibited absorption rates similar to those of the lyotropic series when absorbed by unsaturated colloids. Dandy and Rowntree, in comparing the rates of absorption of dye from the peritoneum of animals in various postures, concluded that with the pelvis in a dependent position there was 15 per cent less absorption than in other postures. Costain, believing that the important route of absorption from the peritoneal cavity was through the thoracic duct, made a thoracic duct fistula for the treatment of peritonitis. McGuire and Cox and Bell, however, in repeating this experiment with a larger series of animals, failed to find lymphaticostomy of value in reducing the mortality rate in experimental peritonitis.

Handley has recently suggested that the severe toxemia of peritonitis is due not so much to material absorbed from the peritoneum as to poisons absorbed from the interior of the gastrointestinal tract, in which there is almost complete stasis as a result of paralytic ileus.

The preponderance of evidence in the literature seems to indicate certain conceptions of peritoneal absorption as being adequately substantiated and generally accepted. Fluids and fluid solutions seem to be absorbed chiefly by the subperitoneal capillaries directly into the blood stream. Suspensions and particles, such as lamp black and bacteria, seem to be absorbed chiefly by the lymphatic system, especially those channels leading to the anterior mediastinal and sternal lymph nodes.

Method of Experimentation. Male rabbits weighing about 2 kg. each and female dogs weighing about 10 kg. were selected because of the ease with which they may be catheterized. Animals were gently restrained in the dorsal posture on suitable tables for observation. For all operative procedures ether anesthesia and aseptic technique were employed.

Several dye solutions were tried, but phenolsulphonephthalein was used as a routine because it can be easily and accurately detected in the urine following its injection intravenously and intraperitoneally. One cubic centimeter of the standard solution (0.6 gm.

dye for 1 cc. of solution) was used for all injections. From 10 to 15 cc. of sterile water was added to the routine intraperitoneal injections in order to promote diffusion of the dye to all peritoneal surfaces.

Animals were catheterized with small, soft, rubber catheters, the bladder washed out and a few cubic centimeters of sterile water left in the bladder with the catheter clamped off. This water was withdrawn and returned to the bladder with a syringe at intervals of one minute. Each time a few drops were tested in alkali for the appearance of the dye. In this way very small traces could be readily detected by inspection.

All animals were used first for control experiments. The dye was injected intraperitoneally and the time between its injection and subsequent detection in the urine recorded. This was verified usually two or more times with each animal. In the first experiments all animals, both before and after production of peritonitis, were given both intravenous and intraperitoneal injections of the dye, but the speed of excretion of dye was found so constant in all cases following intravenous injection that its use was discontinued.

After the control experiments had been completed some of the animals were used for studying the rate of absorption and elimination of the dye, in the presence of bacterial peritonitis. This was induced by injecting bacterial cultures into the peritoneum or by directly infecting it at laparotomy. In several of the dogs ordinary operations, such as gastroenterostomy, were performed and the peritoneum soiled with the intestinal contents, in order to simulate conditions giving rise to peritonitis in the human subject. In others mechanical peritonitis was caused either by intraperitoneal injection of irritants, such as aleuronot and iodized starch, or by massaging the visceral and parietal peritoneum with dry gauze sponges at operation. After peritonitis had developed the animals were given intraperitoneal injections of the dye daily as described. The presence and course of the peritonitis were followed in surviving animals at intervals of three or four days by exploratory laparotomy, and finally the condition of the peritoneum at necropsy was carefully noted.

Results. In several rabbits the dye was injected intravenously both before and after the onset of peritonitis. The time from the injection to the detection in the urine was between four and five minutes in every case.

In two series of rabbits various quantities of sterile water, 15 cc., 30 cc. and so forth, up to 150 cc., were injected intraperitoneally. With the injection of 15 cc. of water it was found that the time between injection and detection of dye in the urine was slightly shortened. Large amounts lengthened the time, the greatest lengthening occurring with 105 cc., above which the time gradually decreased. By washing out the bladders of several rabbits at

various intervals following intraperitoneal injection of dye it was found that all the dye was excreted in from six to eight hours.

The dye was injected intraperitoneally in one group of rabbits in various postures. The time of absorption and detection in the urine was not appreciably altered in any of the experiments.

In another group of experiments 50 cc. of a hypertonic (50 per cent) sucrose solution was injected intraperitoneally with the 1 cc. of dye. In spite of the fact that such a solution takes up fluid from the peritoneum and almost doubles its volume within an hour, it failed in these experiments to alter the time of appearance of the dye in the urine.

There were 36 experiments on absorption of the dye from the peritoneum of normal rabbits. Conditions were standard, as described, and all observations were made by me. The average time between the intraperitoneal injection of the dye and its detection in the urine was eleven and five-tenths minutes. The mean variation from this average was one and nine-tenths minutes, the greatest variation four and five-tenths minutes.

There were 13 experiments on dye absorption in rabbits with mechanical peritonitis. Conditions were standard, as in the group of normal animals, and the presence of mechanical peritonitis was verified by exploration or necropsy. The dye was injected at intervals from one hour to nine days after the production of peritonitis. The average time of detection of the dye in the urine was eleven and three-tenths minutes. The mean variation from this average was one and six-tenths minutes, the greatest variation three and seven-tenths minutes.

There were 23 experiments on dye absorption in rabbits with bacterial peritonitis. Conditions were standard as in the preceding two groups, and the presence of bacterial peritonitis was verified by exploration or necropsy. Injections were made at intervals of from three hours to seven days after the production of peritonitis. In 18 of the experiments the rates of absorption of dye were fairly constant, and in these the average time of detection of dye in the urine was eleven and eight-tenths minutes. The mean variation from this average was one and nine-tenths minutes, and the greatest variation four and eight-tenths minutes. In the other 5 experiments the absorption times were twenty-nine, thirty-six, eighteen, nineteen, and eighteen minutes respectively. In these 5 experiments adhesive peritonitis was present and the area of peritoneal surface available for absorption was greatly diminished.

In order to provide further data on absorption from the normal and infected peritoneum a series of dogs was used. There were 11 experiments on absorption from the normal peritoneum; in these conditions were standard. The average time between intraperitoneal injection of the dye and its detection in the urine was nine and six-tenths minutes. The mean variation from this average was

one and three-tenths minutes, and the greatest variation two and six-tenths minutes. There were 50 experiments on peritoneal absorption in dogs with bacterial peritonitis. Conditions were standard, and the presence of bacterial peritonitis was verified by exploration and necropsy. Injections were made at intervals of from one to fourteen days after the production of peritonitis. The average time of detection of dye in the urine was nine and three-tenths minutes. The mean variation from this average was one and seven-tenths minutes, and the greatest variation four and five-tenths minutes. In the experiments in which the absorption time was longer than the average adhesive peritonitis was present and the area of peritoneal surface available for absorption was greatly diminished.

Experiments on dogs were more satisfactory than those with rabbits. A typical example of the usual experiment is shown in the tabulation:

PROCEDURES AND FINDINGS IN A TYPICAL EXPERIMENT.

1925.	Procedure.	Interval before recovery of dye (min.).	Remarks.
May 5 . .	Injection of dye	8	
May 6 . .	Laparotomy; infection of peritoneum		
May 7 . .	Injection of dye	7	
May 8 . .	Injection of dye	8	
May 10 . .	Laparotomy; exploration; further infection		Moderate grade of peritonitis present
May 11 . .	Injection of dye	9	
May 12 . .	Injection of dye	9	
May 13 . .	Laparotomy; exploration; further infection		Severe grade of peritonitis present with considerable pus and many early adhesions
May 14 . .	Injection of dye	7	
May 15 . .	Injection of dye	9	
May 17 . .	Injection of dye	8	
May 19 . .	Injection of dye	11	
May 20 . .	Injection of dye	7	
May 22 . .	Injection of dye	10	
May 25 . .			Condition of animal poor for one week; now improving
June 2 . .	Injection of dye; laparotomy; exploration	8	Animal in good condition; many adhesions; no exudate or inflammation found; apparently severe peritonitis previously because of the numerous adhesions and thickening of peritoneum

Discussion. The injection of hypertonic solution of sugar intraperitoneally with the dye did not alter the time of appearance of the dye in the urine. Interchange of material must have been tak-

ing place simultaneously, both from the peritoneum into the blood and from the blood into the peritoneum. From these data the intraperitoneal injections of hypertonic solutions to retard absorption seems hardly justifiable as a treatment for peritonitis.

A comparison of the absorption rates of the dye from the peritoneum of normal rabbits, of rabbits with mechanical peritonitis and of those with bacterial peritonitis shows little difference. The average rate of absorption in rabbits with mechanical peritonitis was almost exactly the same as the average rate in normal rabbits. In rabbits with bacterial peritonitis, if those with the adhesive type of peritonitis are excluded, the average rate was almost exactly the same as in normal rabbits. The amount of variation in all three groups is essentially the same and the figures are, therefore, comparable.

There was very little difference in the findings in dogs and rabbits. The average absorption rates were almost exactly the same in normal dogs and in dogs with marked bacterial peritonitis. Occasionally the absorption rate was slightly longer than the average, but this seemed adequately explained by the presence of an adhesive type of peritonitis which had greatly lessened the area of peritoneal surface.

Summary. A brief review of the literature calls attention to the more generally accepted conceptions of peritoneal absorption.

Experiments on rabbits and dogs show that phenolsulphonephthalein is absorbed at essentially the same rate from the inflamed and the normal peritoneum, both in mechanical and bacterial peritonitis.

An exception noted was that an adhesive type of peritonitis greatly lessening the peritoneal area did seem to retard the rate of absorption slightly.

It was further concluded that the presence of hypertonic solution of sugar in the peritoneum did not retard the absorption of dye.

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THE SUCCESSFUL TREATMENT OF RESISTANT WHIPWORM INFESTATION.

With Observations on Overlooked Symptoms.

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Insufficient attention has been given by gastroenterologists, or, for that matter, by the profession in general, to either the direct or indirect role played by intestinal parasites in the causation of morbid states of mind and body. Particularly is this true of infestation with the whipworm (Trichuris trichiura or Trichocephalus dispar). In his textbook on parasitology Stitt[1] remarks: "Whipworms do not, as a rule, produce serious symptoms. The patient may harbor parasites in considerable numbers for a long time without inconvenience. Rarely there may be a symptom-complex with severe anemia, pronounced nervous symptoms and gastrointestinal symptoms." Chandler[2] states that: "Although the whipworm

feeds on blood to some extent, and undoubtedly produces toxins, as evidenced by the increase of eosinophiles in the blood which nearly always occurs in case of whipworm infection and by the occasional mental disturbances or other nervous symptoms, this worm usually produces very slight, in fact, often unnoticeable effects." He further states that: "With the possible exception of hookworms and ascaris, the whipworm is the most common worm parasite in man."

The following paper is based on a study of 11 cases collected over a period of five years. In only 1 case did the patient's symptomatology arouse a suspicion of parasitism, and this was one of the last cases studied. The other 10 cases were simply accidental findings in routine feces examinations of patients suffering from various symptoms.

The only clue to the existence of whipworm infestation is the presence in the feces of dark-colored, oval-shaped eggs with knobs at either pole. The eggs contain the embryo. They are extremely resistant to most antiseptics and with sufficient moisture the egg embryo may live for years. The use of "night soil" as fertilizer is a potent way of contaminating food products. The mode of infection is through swallowing the ova. There is no multiplication of the worm within the body. The worm embryo arrives at maturity one month after ingestion, at which time it may produce eggs. The female whipworms outnumber the males and are somewhat larger than the latter which are less than 2 inches in length. The terminal portion of the worm is thread-like and usually curled up in a spiral. This whip-like portion burrows into the mucosa, thus making it very difficult to rid the intestine of the parasites. It is rarely that one finds the whipworm in the feces. The writer has seen them on several occasions during autopsies. The most common habitat of the whipworm is the cecum, but it is frequently found in other parts of the large bowel. It is supposed to be a frequent cause of appendicitis, though this is questionable. It seems highly probable that injury to the cell membrane by intestinal parasites either chemically, by means of both their secretions and excretions, or mechanically, by their sucking mechanism, allow toxic amines and bacteria or their poisons to enter more readily the circulation.

In the study of our 11 cases of whipworm infection it was noted that nervous symptoms were common to all. The series included 1 case of cholecystitis, 5 cases of chronic colitis—1 of which had multiple myeloma—and 1 case of diverticulosis. The remaining 4 cases showed no clinical pathology, though their symptoms would classify them as gastrointestinal invalids. These patients were all nervous high strung individuals, 4 of whom had consulted neurologists, who diagnosed their cases variously as neurasthenia, psychoasthenia, anxiety neurosis and hypomania. All of these patients

had capricious appetites, though, curiously, underweight was present in but 4 of the cases. All had gastrointestinal symptoms, such as marked flatulency, intestinal colic, constipation or mild diarrhea. One patient occasionally suffered from angioneurotic edema. Urticaria had occurred in 7 of the 11 cases. All patients showed marked pallor, and 2 showed a curious erythema covering the face and chest. Blood pressures were consistently low in all but the patient with cholecystitis. Abdominal examination revealed marked tympany in most instances and the cecal splash was present in every case. Proctoscopic and sigmoidoscopic examinations showed in most of the patients an injected, mottled mucosa streaked with mucus.

Stool Examination. In 9 cases the eggs were easily found. In the other 2 cases eggs were found only after repeated examinations by Barber's glycerin salt method.

Treatment. The time honored methods of parasite eradication by means of anthelmintics failed in all but 3 of our cases. Possibly this was due to the fact that all cases were in adults and infestation had either existed for a long time or was present in an intestine in which there were definite intestinal lesions. Oil of chenopodium with castor oil was tried in 4 cases with 1 cure after two trials. Hall and Foster's chloroform castor oil mixture was used in 7 cases, with 2 cures. The patients who were cured by the oral administration of drugs were those with acute symptoms and with no intestinal lesions discoverable by Roentgen ray or sigmoidoscopic examinations.

Our therapeutic hint which resulted in the cure of our 8 cases resistant to orthodox treatment was based on the assumption that the hair-like projection of the whipworm was embedded in mucous and possibly in the mucosa as well, and thus beyond the reach of drugs taken in the ordinary way. Our technique is briefly as follows:

At the beginning of treatment the patient is given 2 ounces of castor oil and then placed on a low residue diet. Then on each of four successive days he is given a 2-liter enema with 0.5 per cent solution of monohydrated sodium carbonate, to which is added 1 ounce of colloidal kaolin. Kaolin is also given by mouth in 1-ounce doses once daily on each of the above days. The alkali is given for the purpose of dissolving the mucus. The kaolin tends to cut the thicker mucus and mechanically "de-mucuses," so to speak, the wall of the entire colon. The kaolin likewise, by its mechanical adsorption, tends to sediment the bacteria which might possibly form a coating about the parasites. After this four day treatment the kaolin is discontinued, but the alkaline enema is continued for two days or more. After complete expulsion of this enema 8 ounces of crude oil is injected into the rectum through a large syringe and the patient instructed to retain it as long as possible. Proof that this small volume of oil reaches the cecum or even higher up is evidenced by the fact that for three or four days afterward the

patient continues to pass crude oil. In 2 cases fluoroscopic observations were made after the injection of a barium oil enema, and the preparation was seen to readily enter the cecum.

The results of treatment have been invariably successful in the cases studied. Fecal specimens immediately following the treatment and those examined a month later showed no eggs whatsoever. Four patients examined a year later showed negative findings. Two of the colitis patients entirely recovered from their colitis symptoms and were found free of all signs of whipworm infestation a year later. Stool examinations were made in 3 cases after the sodium carbonate kaolin enema series and prior to the oil administration, but eggs were still present, indicating that the oil is a necessary adjunct to the cure.

Summary. In the presence of structural change in the alimentary tract whipworm eradication, by means of anthelmintics, is practically impossible. The writer's colonic method was successful in the 8 patients so treated.

In all our cases of whipworm infestation a fairly definite symptom complex existed. Whether the infestation was superimposed upon an already existing pathologic colon, or had an etiologic relation to it, is difficult to say. A more scientific study of the pathology and symptomatology of whipworm infestation in its relation to to alimentary disorders is suggested.

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FURTHER REMARKS ON INFECTION OF THE GALL BLADDER IN RELATION TO CHRONIC (PERNICIOUS) ANEMIA.

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Three years have elapsed since the writing of our former paper, "Infection of the Gall Bladder in Relation to Pernicious Anemia."[1] In that study 13 cases of chronic anemia possessing some or all of the characteristics of idopathic progressive pernicious anemia were discussed. Of this number, 11 cases were recognized as frank per-

nicious anemia. Two cases were called borderline anemia, because megaloblasts were not found in blood smears and because the clinical picture did not present a progressive, or interruptedly progressive, downward course. These 2 cases possessed, however, a megalocytic type of anemia with a plus color index, complete achylia, glossitis and paresthesia. The blood picture differed little from that of the other cases, except in the severity of the anemia. Each of the 13 cases showed the presence of chronic infection of the gall bladder. The character of the infection of the gall bladder—and presumably that of the entire biliary tract, so far as could be determined—possessed no evidence of specificity.

The purpose of this report is to summarize briefly the subsequent histories of those patients upon whom cholecystectomy was performed, to add some data of further observations made upon similar patients and to state some general conclusions which the study seems to warrant.

Case Reports.—Former Series. CASE I.—(Borderline anemia.) Mrs. G., was readmitted in June, 1924, deeply jaundiced. The common bile duct was drained, and the patient made a slow recovery. Following the operation the blood counts dropped to 42 per cent hemoglobin* (Sahli-Haskins[2]); 3,380,000 erythrocytes and 7800 leukocytes, with many polychromatophilic red blood cells. In December, 1924, the patient had partially regained her former strength, but still showed a marked secondary anemia. The hemoglobin was 67 per cent; erythrocytes, 3,840,000; color index, 0.87; volume index, 0.96; leukocytes, 4750. There were no abnormal red blood cells present. Therefore, during the seven years following her first gall bladder operation there has been no return of her previously existing megalocytic anemia with a plus color index. In the summer of 1925 the jaundice returned, together with enlargement of the liver and beginning ascites. Death occurred from progressing chronic obstructive biliary cirrhosis in October of the same year.

CASE II.—Mr. C., following cholecystectomy in September, 1922, recovered partially during the winter of 1922–1923, and returned to his work of "cruising" timber. The paresthesia of his hands and feet, which had become acute immediately after his operation, disappeared completely for a time during the winter. The patient suffered a relapse in the late spring of 1923 and died in September of the same year. His blood examination prior to his death showed a true megaloblastic anemia of severe grade.

CASE III.—(Borderline anemia.) Mrs. K. has remained well since her operation in January, 1923. The blood continues to show the picture of secondary anemia, but the megalocytic character of it, which existed previous to her cholecystectomy has not returned. In November, 1924, her blood examination showed 64 per cent hemoglobin (Sahli-Haskins method); 4,050,000 erythrocytes; color index, 0.80; volume index, 0.92; icterus index, 5.7; 5500 leukocytes. The patient has experienced no paresthesia and the soreness of the tongue has disappeared.

* The figures for the percent of hemoglobin in the patients of the second series are not the direct readings of the Sahli-Haskins hemoglobinometer (on this instrument 100 per cent corresponds to 13.8 gm. of hemoglobin in 100 cc. of blood), but are so calculated that 100 per cent corresponds to 14.7 gm. of hemoglobin per 100 cc. of blood, the normal hemoglobin coefficient determined by Osgood.

TABLE I.—SEVEN CASES OF CHRONIC ANEMIA, SPOKEN OF IN TEXT AS BORDERLINE ANEMIA, WHICH CLINICALLY RESEMBLED MILD PERNICIOUS ANEMIA, BUT WHICH UNDERWENT SYMPTOMATIC RECOVERY AFTER REMOVAL OF INFECTED GALL BLADDER.

(Note Similarity of Clinical Data to Those of 4 Cases of Pernicious Anemia Listed in Table II.)

Case.	R. B. C. in millions.	Hb., per cent.	Macrocytosis polychromatophilia.	Nucleated red cells.	Color, Index.	Volume index.	Icterus index.	Achylia.	Glossitis.	Paresthesia.	Duration of illness before operation.	Postoperative notes.
Case I	3.68	85 (Dare)	+	0	1.16	....	....	+	+	+	7 years	
(Series I)	5.25	70 "	0	0	0.76	....	....	+	0	0		Blood examination 9 months postoperative
	3.84	64 (S. H.)	0	0	0.88	0.96	....	+	0	0		Blood examination during obstructive jaundice
Case III	3.99	80 (Dare)	+	0	1.02	....	....	+	+	0		
(Series I)	5.09	70 "	0	0	0.70	....	....	+	+	0	1 year	Blood examination 2 months postoperative
	4.05	64 (S. H.)	0	0	0.80	0.92	5.7	+	0	0		Blood examination 20 months postoperative
	4.06	66 "	0	0	0.80	0.96	6.4	+	0	0		Blood examination 3 years postoperative
Case I	1.38	15 "	+	+normoblasts	0.55	....	....	+	0	0		Blood examination after transfusion
(Series II)	2.21	46 "	+	0	1.00	1.20	2.0	+	0	0	3 years	Death 4 days postoperative
Case II	3.10	63 "	+	0	1.00	1.20	5.0	+	0	0		
(Series II)	3.71	67 "	0	0	0.90	0.96	5.0	+	0	0	9 months	Blood examination 1 month postoperative
	4.36	75 "	0	0	0.87	0.87	3.6	+	0	0		Blood examination 10 months postoperative
Case III	3.90	86 "	+	+normoblasts	1.10	1.20	9.1	+	0	+		
(Series II)	4.68	89 "	tr.	0	0.96	0.99	6.9	+	0	+	2 years	Blood examination 1 month postoperative
	4.11	83 "	0	0	1.01	1.02	10.0	+	0	0		Blood examination 1 year postoperative
Case IV	3.85	50 "	+	0	0.65	1.10	8.7	−	0	+	Several	
(Series II)	4.28	65 "	tr.	0	0.77	1.07	6.6	−	0	0	years also	Blood examination 1 month postoperative
	4.32	70 "	0	0	0.81	0.83	6.8	−	0	0	O. H. D.	Blood examination 9 months postoperative
Case V	4.14	50 "	+	0	0.60	0.85	6.0	−	+	0	4 years to-	No change of anemia symptoms after hysterectomy
(Series II)	4.52	62 "	0	0	0.68	0.75	3.6	−	0	0	gether with	Blood examination 1 month after cholecystectomy
	4.26	86 "	0	0	1.01	1.02	6.7	−	0	0	uterine hem-	Blood examination 11 months after cholecystectomy
											orrhages	

CASE IV.—Mr. H. was operated upon in May, 1923, and, as previously reported, a chronic infected gall bladder was removed. He recovered from the operation and returned to light farm work, but his blood never lost its megalocytic character. The soreness of the tongue disappeared; the numbness of his hands and feet, however, persisted. The patient suffered a relapse in February, 1924. He is still living, but has not been seen since this time.

CASE V.—Mrs. J., after having experienced the same symptomatic improvement in her general health noted by the other patients suffering from pernicious anemia following cholecystectomy, relapsed in October, 1923, and died early in the winter of 1924. The soreness of the tongue never returned.

We now give a brief description of 9 more cases of chronic anemia. Five of them we have placed in the borderline group and 4 we have considered true progressive pernicious anemia. Each case possesses a definite megalocytic anemia; anisocytosis, deformed cells and polychromatophilia. Two cases in the borderline group showed normoblasts in the blood stream; none of the cases in the pernicious group revealed any megaloblasts in many blood smears studied. A plus volume index was present before operation in all but 1 patient. The clinical data is given briefly in the subjoined tables:

Borderline Group.—New Series. CASE I.—Mrs. J., aged forty-eight years, a housewife, had been anemic and ill for three years. The illness became more acute in July and she was received in the hospital, August 4, 1924. She had the lemon tinted skin and the general appearance of pernicious anemia. Normoblasts were found in the blood stream, and the volume index was 1.2 on several occasions. Repeated blood transfusions raised the blood strength to 65 per cent hemoglobin and 3,000,000 red blood cells. A slow, continuous bleeding from some unrecognized point in the intestinal tract was present. The roentgenologic evidence of a diseased gall bladder was also obtained, and she was operated upon, September 20. The gall bladder was thick walled with many large, soft glands along the ducts; the appendix was thick walled and contained fecal stones; there were several small nontraumatic, hemorrhagic areas along the mesenteric side of the upper intestine from which the bleeding was taking place. The mesenteric glands were large and many of them calcified. Death followed on the fourth day. No autopsy was obtained.

Pathologic report: A pure culture of hemolytic streptococcus was obtained from the gall bladder. The appendix was atrophied.

CASE II.—Mrs. C., aged twenty-five years, a housewife, became pale and weak three years before, during a pregnancy. Her illness had slowly progressed until she had become completely incapacitated. She had the lemon tinted skin of pernicious anemia of moderate severity, but glossitis and paresthesia had not been present. Her teeth had been recently extracted for pericemental sepsis. The roentgenologic evidence of a diseased gall bladder was obtained and she was operated upon, January 6, 1925. The gall bladder was large, dirty grayish in color and contained stones. There were no other lesions noted in the abdomen. The gall bladder and a piece of liver were removed. The appendix had been removed at a previous operation.

TABLE II.—FOUR CASES OF PERNICIOUS ANEMIA CHARTED TO ILLUSTRATE SYMPTOMS SIMILAR TO THOSE OF CASES NOTED IN TABLE I.

Case.	R. B. C. in millions.	Hb., per cent.	Macrocytosis polychromatophilia.	Nucleated red cells.	Color index.	Volume index.	Icterus index.	Achylia.	Glossitis.	Paresthesia.	Duration of illness before any treatment.	Posttreatment notes.
Case VI . . .	2.93	70 (S. H.)	+	0	1.20	1.30	8.0	+	+	0		Patient remains in fair health; able to work
(Series II)	4.04	84 "	+	0	1.05	1.05	7.8	+	+	0	1 year +	Blood examination 1 month after cholecystectomy
	3.95	85 "	+	0	1.07	1.19	5.6	+	+	0		Blood examination 9 months after cholecystectomy
	3.70	90 "	+	0	1.20	1.30	5.7	+	+	0		Blood examination 14 months after cholecystectomy
Case VII . .	2.20	59 "	+	+normoblasts	1.30	1.40	6.2	+	+	+		Cord degeneration progressing
(Series II)	3.48	79 "	+	0	1.16	1.05	7.6	+	+	+	1 year	Blood examination 3 months after cholecystectomy
	3.40	83 "	+	0	1.20	1.20	6.7	+	+	+		Blood examination 3 months after splenectomy
	2.40	60 "	+	..	1.25	1.36	8.1	+	+	+		Blood examination 9 months after splenectomy
Case VIII . .	3.41	70 "	+	0	1.00	1.40	6.2	+	+	+		Death from progressing anemia
(Series II)	3.54	75 "	+	0	1.00	1.10	6.6	+	+	+	1 year	Blood examination during medical treatment
	3.18	75 "	+	0	1.20	1.20	8.1	−	+	+		Blood examination during second relapse, 2 months before death
	0.80	22 "	+	0	1.37	....	....	−	+	+		Blood examination 1 day before death
Case XI . . .	2.59	65 "	+	0	1.35	1.70	10.0	+	+	+		Death from progressing anemia 1 year later
(Series II)	2.90	79 "	+	0	1.30	1.40	10.7	+	+	+	2 years	Blood examination during medical treatment

Pathologic report: Chronic interstitial cholecystitis with fibrosis, scarring and lymphoid infiltration. Fatty or parenchymatous degeneration of marked degree of the liver; chronic interstitial hepatitis.

Cultures of the gall bladder wall and liver gave Staphylococcus albus in each.

Symptomatic recovery has taken place, but a moderate anemia of secondary type remains.

CASE III.—Mrs. B., aged forty-four years, a housewife, was first examined in 1917 because of a general asthenic state. Complete achylia gastrica was found at that time. In January, 1925, she returned because of numbness and tingling in the upper jaw and in both hands and feet. These symptoms had begun two years before, two months after the extraction of an abscessed right upper molar tooth. There had been no soreness of the tongue. Complete achylia was again found to be present. Roentgenologic evidence of a diseased gall bladder was obtained, and cholecystectomy and appendectomy were performed, January 28, 1925. The gall bladder was thick walled and adherent to the surrounding organs. The appendix was long and contained many fecal stones. The patient's health at time of writing (January, 1926) is quite normal. The numbness of the hands and feet disappeared quickly after operation. There have been no symptoms of glossitis.

Pathologic report: Chronic catarrhal cholecystitis. Fibrosis and hyalin degeneration of the appendix. No bacterial growths were obtained in cultures from the gall bladder and liver.

CASE IV.—Mrs. P., aged sixty-three years, a housewife, had been pale and weak for a number of years. She had suffered also for several years with dyspnea on moderate exertion in relation to a rheumatic mitral heart disease with auricular fibrillation without failure. Recently she had been confined to bed because of extreme exhaustion. The type of her anemia and the lemon tinted paleness of the skin made us suspect the presence of an underlying gall bladder disease. Stomach analyses were not made because of the presence of the heart disease. Definite numbness and tingling of the feet were present. There was no bleeding from the bowel. The patient was kept in bed for some time under dietetic and medicinal treatment for the anemia without benefit. On January 8, 1925, the gall bladder and appendix were removed. The former was thick walled and much enlarged; the common duct was dilated. A year has elapsed since operation. The patient is now stronger and in better health than she has been for years. The skin is clear and the lemon tint has disappeared. The heart action has quieted down; she no longer needs digitalis to control the auricular fibrillation. A moderate anemia still persists, but the megalocytic character of the red blood cells has disappeared and the volume index has dropped from 1.1 to 0.83.

Pathologic report: Atrophy and scarring of the gall bladder wall. Subacute purulent appendicitis of moderate grade, involving especially the mucosa, with plasma cell hyperplasia of the lymphoid tissue.

CASE V.—Mrs. C., aged forty-three years, a housewife, had been ill for seventeen years with mucous colitis. Diseased teeth and tonsils had been removed. In recent years she had become weaker and paler because of periodic bleeding from multiple myofibromata of the uterus. Her paleness was lemon tinted, however, and not of a whiteness due to bleeding. The tongue has been definitely sore at times, but no paresthesia has been present. Evidence of gall bladder disease was found roentgenologically. A supravaginal hysterectomy and appendectomy were performed on February 12, 1925, at which time the diagnosis of chronic cholecystitis was verified. The anemia and lemon tinted color of the skin did not improve

after operation. The patient remained weak; her convalescence was slow. Cholecystectomy was performed, March 27. Her response then was noticeably different from that following the first operation. Her skin cleared quickly and she improved rapidly in general health. The anemia, however, was slower to overcome. The soreness of the tongue disappeared and has not returned. She is in better health now than for years.

Pathologic report: Catarrhal and indurative cholecystitis. Cultures of the gall bladder wall gave a nonhemolytic streptococcus.

This patient differs from the other 4 patients of the borderline group in that the blood volume index has always been low, and also probably in the fact that ferments may have always been present in the gastric juice. Stomach analyses were not made during the acute period of the patient's illness. Later a normal stomach chemistry was found to exist. At the same time the blood volume index and the color index had returned to normal. This return to a normal blood picture has not been observed in the other cases. Whether there is a relation between the recovery of the normal blood picture and the absence of achylia is not known.

We have now under observation another patient of similar type: A man, aged fifty years, who has been anemic and ill for two years. He suffers from weakness, dyspnea on exertion, periodic soreness of the tongue, numbness of the fingers and periodic nausea, vomiting and pain in the abdomen. His case has the appearance of pernicious anemia, and his illness has been so considered by some physicians whom he has consulted. His blood examinations give, on an average, the following figures: Hemoglobin, 46 per cent; red blood cells, which are very irregular in size and shape, 2,700,000; white blood cells, 7000; color index, 0.85; volume index, 0.86; icterus index, 2.2 (in spite of the presence of chronic cholecystitis). The fasting stomach contains free hydrochloric acid and no food remnants. An Ewald breakfast shows 55 free hydrochloric acid and 74 total acidity, with well chymified food. No improvement in the patient's condition could be brought about by medical treatment in hospital, and as positive roentgenologic evidence of a diseased gall bladder was obtained, cholecystectomy has recently been done.

The 4 remaining cases of this series are examples of true progressive pernicious anemia. They differ from the others clinically, however, only in the degree of anemia, and, in the 2 patients upon whom cholecystectomy was performed, in the failure of noticeable relief after operation. The blood volumes also ranged higher in these patients and did not drop so low after operation; but, again, this variation may be but a matter of degree.

Pernicious Anemic Group.—New Series. CASE VI.—Mrs. E., aged fifty-one years, a housewife, was seen first in January, 1925. She had been pale for years, but during the past year the paleness had increased, soreness of the tongue had appeared and she had lost in weight and strength. On examination, the patient showed the presence of glossitis, complete achylia and a megalocytic blood picture. The roentgenologic evidence of a diseased gall bladder was obtained, and this organ, together with the appendix, was removed, February 17, 1925. The gall bladder was thick walled, with many small papillæ like nodules growing into its lumen. The common duct was not enlarged, but there were many soft glands along its course. Cultures of the gall bladder wall were sterile, except for four colonies of a short Gram positive bacillus. A piece of liver cultured showed several colonies of Staphylococcus aureus. Specimens of stool and scrapings from the tongue were cultured for yeast, being grown on a modified Sabouraud

medium, as suggested by E. J. Wood.[3] From each source yeast cells were obtained which were grossly, microscopically and culturally identical. After forty-eight hours culturing at 30° C. small, yellowish white, glistening colonies appeared, which, microscopically, showed large, rapidly growing yeast cells with many buds but no hyphæ. Culturally on sugars they reacted as follows: Maltose, acid, no gas; lactose, negative; glucose, negative; litmus milk, coagulated. The organism was not considered Monilia psilosis.

Since the operation the patient has improved very much in health and strength. Her skin has cleared and the lemon tinted color has disappeared. She is not as well or as strong as she was two years ago. The glossitis comes and goes. She has never suffered from paresthesia. Many macrocytes remain in the blood stream and the blood volume remains slightly above 1.

Pathologic report: Chronic cholecystitis. Moderate atrophic appendicitis.

CASE VII.—Mr. P., aged sixty-six years, a merchant, was first examined in 1914, when a complete achylia gastrica was found. On a corrective diet and hydrochloric acid he became free of symptoms and remained well until one year before he returned for reëxamination in January, 1925. For a year he had been losing weight and strength. He had become pale, short of breath and periodically had suffered from numbness and tingling in the hands and feet and soreness of the tongue. His skin was pale and lemon tinted in color; his tongue slick with reddish patches; the achylia was still present; his blood was macrocytic in type with a volume index of 1.4 and occasional normoblasts. The reflexes were normal. Roentgenologic evidence of a diseased gall bladder was obtained, and he was operated upon, February 16, 1925. The gall bladder was thick walled and adherent to the hepatic flexure of the colon and the duodenum. The spleen was much enlarged. It was estimated to be about four times its normal size. The gall bladder and appendix were removed at this time. Following the operation the blood picture did not change much in its appearance, although the hemoglobin reached 88 per cent and the red cell count 4,000,000 per cubic millimeter. The color of the skin cleared a good deal, though not as it had in the other patients. A moderate relapse began in the summer, so that it was thought justifiable to remove the spleen. This was done, August 10, 1925. The spleen was now found to be about one-third its former estimated size as seen in February.

Since the last operation the patient's convalescence has been about as it was after the cholecystectomy. The skin is much clearer and the lemon tinted color has nearly disappeared, but aside from this fact there is little change. The anemia and the glossitis remain as before. The degenerative cord changes are progressing. Megaloblasts have never been found in the blood. He is now receiving blood transfusions.

Cultures made from the gall bladder on blood agar plates and in blood dextrose broth gave colonies of Staphylococcus albus. Similar cultures from the spleen gave hemolytic Staphylococcus aureus and Staphylococcus albus. Cultures were also made in this patient from tongue scrapings and from the stool as in Case VI. Microscopically the yeast obtained in these cultures resembled very closely that obtained in the latter case, but had a different reaction upon the sugars. There were no demonstrable hyphæ present. After forty-eight hours' incubation at 30° C. small, whitish, glistening colonies appeared. Microscopically, large celled, rapidly budding yeast cells without hyphæ were seen. Culturally, on sugars, the following occurred: Lactose, negative; maltose, acid and gas; dextrose, acid and gas; milk, no change. Seemingly the same organism was obtained from both the tongue scrapings and from the stool. It, likewise, was not considered to be Monilia psilosis.

Pathologic report: Chronic cholecystitis. Slight diffuse chronic hyperplasia of the spleen.

CASE VIII.—Mrs. R., aged sixty-seven years, a housewife, was first under treatment in 1914 for a general asthenia in relation to a complete achylia gastrica and constipation. The last few years she has had occasional pain of slight degree under the right costal margin. Myositic pains of the neck and left shoulder girdle ceased after the removal of her tonsils and several devitalized teeth one year ago. She was reëxamined and under hospital treatment in August, 1924. For over a year she had complained of dyspnea on exertion and slowly increasing general weakness. She has had periods when her tongue was sore, but had had no sensory disturbances. Her blood picture was megalocytic in type. The blood volume was at first 1.4, but returned to 1.1 under bedrest, arsenic, and so forth, during which time she also improved much in general health and strength. In December, 1925, she suffered a relapse, during which time sensory disturbances became marked, and her blood picture was: Hemoglobin, 42 per cent; red blood cells, 1,960,000 without nucleated cells; volume index, 1.6; color index, 1.2; icterus index, 6.6. Death occurred a few weeks later. Autopsy was not obtained. The roentgenologic evidence of a chronic gall bladder disease was present. It is interesting, furthermore, to note that the patient was a sister of the patient, Case XI, of the first series, and that a second sister is now ill with pernicious anemia with marked cord changes. (See papers of Meulengracht[4] and others.)

CASE IX.—Mr. S., aged sixty-two years, a business man, was under examination and treatment in the summer of 1924. His case is cited because it was a frank, rather rapidly progressing type of pernicious anemia with marked degenerative cord lesions, without, however, a megaloblastic type of anemia, and with positive roentgenologic evidence of chronic gall bladder disease obtained on two different examinations. The patient died in August, 1925. Autopsy was not obtained.

Discussion. In the description of the two groups of anemia patients recorded in this paper and in the former paper, a marked similarity in the type of anemia and in the physical findings on examination is noted. A chronic lytic anemia existed in each patient except for the presence of megaloblasts, which were found in only 3 of the 21 patients studied clinically during life. The skin of each patient showed lemon tinted paleness and in all except 1 patient achlorhydria was present. Glossitis occurred 13 times and subjective symptoms of cord changes were experienced 14 times. Evidence of a diseased gall bladder were found by roentgenologic methods in each patient examined clinically, and these findings were verified by the pathologist in the patients coming to operation. Disease of the biliary tract was found also in the cases which came to autopsy.

More upon intensity of the symptoms than upon difference of clinical picture, the cases were divided into two groups, namely, those of frank progressive pernicious anemia and those which we have spoken of as borderline anemia. We called the picture a borderline anemia because the blood was megalocytic in type, because other causes for the anemia were not found and because the patients did not progress to a fatal issue after cholecystectomy,

but returned, on the other hand, to fairly normal health, in which the so-called pernicious characters, as represented by the blood, skin, tongue and sensory disturbances, disappeared. A return of gastric ferments was not observed. (Note that Case V, second series, may be an exception.)

During the study of the first series of cases an attempt was made to produce a chronic anemia in dogs by producing chronic infection of the biliary tract by means of organisms obtained culturally from the gall bladders and livers of some of the patients. Negative results were obtained. Insofar as they could be judged, the organisms seemed to be nonspecific. Similar types of organisms were obtained from patients of the second series. In 2 cases of pernicious anemia tongue scrapings and stools were cultured for yeast, according to the suggestion of Wood. Yeast cells were obtained in each case, but they could not be identified as Monilia psilosis, which has been connected by Ashford with sprue.

The fact that the biliary tract of each patient of both series proved to be infected is of outstanding interest. Whether the infection was simply one of many focal infections existing in the body or whether it has a deeper meaning remains to be proved. As one theorizes about the cause of the two arbitrarily designated anemias, one recognizes the necessity of the presence of some hemolytic agent or agents which operate continuously over a variable length of time, and produce in the pernicious group, at least, hyperplastic changes in the bone marrow. We have not had opportunity to study the bone marrow in any of the cases of the borderline group. To think of these anemias as being the result of widespread focal infections from a dental, a lingual or other source, as some writers have held, is not logical, because such infections are almost universal; but it is logical to believe that an infection, or other disease process, operating in a special way from a special site, may produce such an anemia. The fact that lytic substances causing the pernicious anemias of Bothriocephalus latus and of hookworm infections are said to be lipoid in character, and that a megaloblastic anemia may be caused in rabbits by using a similar agent, suggests the possibility that changes in the cholesterol content of the bile, by means of organisms possessing special properties and operating in constant contact with it, may be a possible cause. The question of hereditary factors as seen in families in relation to a constitutional pathology does not detract from the credibility of such an hypothesis. Unquestionably, however, proof supporting such an hypothesis is wholly lacking. The supposition must rest for the present upon the meager clinical evidence afforded by the study of such cases as these recorded here.

What, then, is the clinical evidence upon which a causative relation between chronic infection of the biliary tract and a chronic lytic anemia may be surmised? In the first place, constant achlorhydria is present. Just what the presence of achlorhydria may

mean is not known, but it seems to be the ground upon which a group of chronic diseases are related. In this category pernicious anemia has always occupied an important place. Again, the anemia is essentially chronic, although variable in its intensity. This variable characteristic of the disease strengthens the belief that one is dealing with the same underlying mechanism in the two groups, for all gradations in symptoms and course are found, from the rapidly fatal pernicious type to the type which causes the patient to drag on through many years, to die finally from true pernicious anemia or to succumb to some intercurrent infection. The cases spoken of above as borderline anemia are of this latter type. There is no clinical means known at present by which a closer differentiation can be made. The volume index of the blood, upon which some writers place much reliance, shows the same variations in degree.

A close scrutiny of the remaining clinical symptoms of the two groups does not lend any aid toward segregation. There is found the same variation in degree in these symptoms that one sees in the progress of the disease itself. The soreness of the tongue comes and goes in patients of each group. The same is true of the sensory disturbances. Both symptoms are only more severe and more persistent in frank pernicious anemia. Periods of relapse and partial recovery occur less noticeably in the borderline group than in the other, but they nevertheless occur. Normoblasts and microblasts occur in the blood stream with moderate frequency in the borderline type and megaloblasts are often entirely absent throughout the course of true pernicious anemia. Aside from the giant nucleated red blood cells, however, there is no difference in the blood picture of the two groups except in degree. A high blood volume index, as first noted by Capps,[6] has been considered to be of special significance in the differentiation of true pernicious anemia from other types of anemia.* In the borderline group a blood volume index

* For the proper interpretation of blood analysis figures clinical methods must be used which reasonably stand the test of research accuracy. The methods employed with the patients of the second series are as follows: (1) Hemoglobin estimation: The Haskins modification of the Sahli hemoglobinometer with which a permanent standard made of an aqueous solution of ferric sulphate and cobalt sulphate is used, the pipette and tubes being correctly calibrated. This method gives results within 2 per cent of the correct amount (J. Biol. Chem., 1923, **57**, 1). (2) Blood volume index: Venous blood, prevented from coagulation with potassium oxalate in proportion of 20 mg. per 10 cc. of blood is centrifuged inaccurately calibrated tubes, at 4500 revolutions per minute, until there is no further change in the volume of the packed cells noted on repeated centrifuging. The specimen is centrifuged in five-minute periods. From thirty to sixty minutes is usually necessary to obtain constant readings. The volume index, according to Osgood, varies between 0.85 and 1.15 in 90 per cent of the bloods of normal men. The color index varies also between 0.85 and 1.15 in similar bloods. (Osgood: Hemoglobin, Color Index, Saturation Index and Volume Index and Volume Index Standards, Arch. Int. Med., **37**, 1926, 685.) (3) Red blood cell counts have all been made on the patients of the second series with the same hemocytometer. These estimations, as well as those of the blood volume and the hemoglobin have been frequently checked, for the sake of greater accuracy, by Dr. Osgood and Dr. Holbrook of the Department of Biochemistry.

of 1.2 is not uncommon, and in true pernicious anemia the same index may be lower than 1.1. In one patient dying of uremia we noted a blood volume index of 1.3 and 1.4. The pathologist's post-mortem findings in this case were cardiorenal disease, arteriosclerotic kidney, fibrinous pericarditis and extreme hyalin degeneration of the spleen, liver and adrenals. There were no noteworthy gross changes in the marrow of the long bones.* The relatively high volume content of the red blood cells may be a group reaction and in no way a specific one.

The response of the patient to removal of the infected gall bladder in both groups is suggestive of a causative relationship. In frank pernicious anemia cholecystectomy may produce a profound betterment for a time. The skin will clear, the glossitis and paresthesia may disappear and the patient will temporarily improve. The blood volume index may drop to 1 or even below 1. The pernicious type of the blood, however, does not disappear. Relapses have occurred as before and death of patients who were operated upon three or more years before has finally resulted from the anemia. In Case VII, in which splenectomy was performed, the previous removal of the gall bladder had a profound effect upon the condition of the spleen.

In the 6 patients of the borderline group removal of the infected gall bladder has had the same beneficial effect upon the immediate clinical picture. The improvement is more pronounced and thus far has been permanent in 5 of the 7 cases listed. One of the remaining 2 patients, after six years of ordinary health, developed a persistent common duct obstruction that resulted in chronic obstructive biliary cirrhosis of the liver; the other patient died shortly after operation from continued bleeding. The remaining 5 patients all have shown the following changes: The skin has lost its lemon yellow color; the blood picture has changed from one with numerous macrocytes, irregularly stained cells, and plus color index, to the picture of moderate secondary anemia; the blood volume index, when it was above normal, dropped below 1 and remained there. Of all symptoms, the anemia has been the slowest to disappear. The soreness of the tongue and the paresthesia have disappeared quickly and have not returned. There has been no return of the previous relapses. The achlorhydria has thus far been persistent. Nevertheless, the patients either consider themselves now well, or feel that, the cause of their illness having been removed, they are becoming progressively better. Data regarding their general

* Histologic examination of the bone marrow in this case shows little or no hyperplasia. There is, however, a greatly increased number of eosinophilic myelocytes and a moderate increase of megaloblasts. There is evidently some blood destruction, but even the increase in megaloblasts is hardly great enough upon which to base a diagnosis of pernicious anemia. The history of the patient during life was that of cardiorenal disease. To correspond with the increase in eosinophilic cells in the bone marrow there was no history, on the other hand, of asthma, or of intestinal parasitism, and three differential blood counts showed no eosinophilia.

appearance, body weight and blood examinations, periodically obtained, substantiate these beliefs.

A study of the patients of the two groups impresses one with the possibility that a mild and a more severe grade of the same disease is being considered. Wood has made the interesting observation that feeding to guinea pigs a culture of Monilia psilosis obtained from cases of pernicious anemia produced a hemolytic blood picture with hyperplastic bone marrow changes; that the filtrate of the culture given intravenously produced the same hemolytic blood picture in less marked degree; that the giving of smaller amounts to the animals produced similar changes, from which the animals recovered when the injections were discontinued.

Pernicious anemia is doubtless a group of diseases. From time to time a specific cause of chronic hemolytic anemia has been recognized, and a small group of cases split off from the main group with unknown causes. It seems to us quite justifiable to suspect that in the segregation of the cases above recorded into true pernicious anemia and borderline anemia, we have been working with a hemolytic type of anemia of unknown cause, but related in some way to chronic infections of the biliary tract; that, by the removal of, possibly, the main focus of infection, mild cases may have recovered; that in the more severely infected cases, which go on to death, the hemopoietic centers of the bone marrow simply may have been damaged beyond repair, or that further extension of the infection in the liver may have permitted the continued formation of the same lytic bodies. The hypothesis that such an infection may cause anemia through changes in the cholesterol content of the bile is attractive.

Conclusions. 1. In every case of pernicious anemia with which we have personally worked during the time of this study, a chronic infection of the gall bladder has been positively demonstrated.

2. A small group of cases, which resembled mild pernicious anemia, possessed the same type of biliary infection, and upon its removal the patients were restored to fairly normal health.

(The pathologic and bacteriologic studies recorded in the above paper were made in the department of pathology under the guidance of Dr. Robert L. Benson, to whom we wish to acknowledge our indebtedness.)

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THE INTRADERMAL SALT SOLUTION TEST IN SCARLET FEVER.*

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The intradermal salt solution test, as described by McClure and Aldrich[1] is carried out by injecting intradermally 0.2 cc. of a sterile 0.8 per cent aqueous solution of sodium chlorid, and recording the time necessary for the disappearance of the wheal so formed. The wheal is considered to have disappeared when it can no longer be detected by light palpation. In normal persons the time required is sixty minutes or more, while in various diseases it is reduced. McClure and Aldrich[1, 2] reported occurrence of shortened disappearance times in children with edematous and preëdematous conditions, especially those with associated albuminuria. Baker[3] found shortened disappearance time in scarlet fever and diphtheria patients; Harrison,[4] in children with lobar pneumonia; Olmsted,[5] in cardiac disease in children. Cohen,[6] and Cohen, Applebaum and Hainsworth[7] used the test as a means of determining the efficiency of the circulation in the extremities in peripheral vascular disturbances of the sort that may lead to gangrene. Lash[8] reported the finding of a markedly shortened time in toxemias of pregnancy. It has been suggested that increased rapidity of absorption of the injected salt solution may be related, in some conditions studied, to tissue intoxication resulting from infection or circulatory disturbance.

Intradermal salt solution tests were carried out on 60 scarlet fever patients. The wheals were observed until they disappeared, unless they persisted longer than sixty minutes. Times of sixty minutes or more were considered normal. A test was made when the patient entered the hospital, usually between the second and eighth day of the disease, and was repeated at intervals of a few days thereafter, usually until the disappearance time became normal. The wheals were made on the arm and leg, or sometimes on the arm alone.

The present series represents cases of scarlet fever of more than average severity, as only a few patients with mild attacks were tested. Most of the patients showed a shortened disappearance time at the first test, with the amount of shortening roughly proportional to the degree of toxemia and the height of the temperature. Those who were only slightly ill with slight elevation of temperature, had normal or nearly normal times. In moderately severe cases the time was usually between thirty and forty minutes. There were exceptions, however; for example, a fairly sick patient,

* This work was done at the Annie W. Durand Hospital of the John McCormick Institute for Infectious Diseases under the auspices of the Otho S. A. Sprague Memorial Institute.

with temperature of 102° F., had a normal disappearance time; one, only mildly sick with temperature of 99.6° F., had a time of twenty-three minutes. In all of the very sick patients, about 10, of either toxic or septic type, the wheal disappeared rapidly, in six to thirty minutes. The shortest time observed was six minutes. This was in an adult who entered the hospital on the sixth day of illness. He was exceedingly toxic, irrational much of the time, with an intense rash, temperature of 104.2° F. and a very low output of urine containing albumin, casts and blood. There was no palpable or visible edema. He died the next day. Three other patients, all very sick, had disappearance times below twenty minutes in the first week of illness. Only one of these had albuminuria and none had palpable edema.

The shortened disappearance times, as a rule, returned rapidly to normal in the absence of complications. Since the tests were not made daily, the first day of normal time is not known, but in uncomplicated cases, in which tests were done at intervals which permit the drawing of conclusions, approximately 75 per cent had reached normal by the eleventh day. Frequently the disappearance time became normal before the temperature, but occasionally this relation was reversed. In only 2 or 3 instances were the patients apparently well and ready to get up, as far as the clinical condition was concerned, before the disappearance time had become normal. In one patient apparently well, in whom the disappearance time seemed slow in reaching normal, whooping cough developed during convalescence from the scarlet fever.

The complications of scarlet fever may not be accompanied by a reduction of disappearance time. Two cases of otitis media and one of arthritis occurred without any reduction. However, the septic patients with high fever and general prostration had shortened times during the febrile period.

A case of moderately severe postscarlatinal nephritis was observed in a boy, aged six years, who had been only mildly sick at first. No tests had been made during the acute stage of the scarlet fever. On the eighteenth day there were blood, albumin and casts in the urine, with a slight rise in temperature. The disappearance time was then forty-three minutes for the arm and twenty minutes for the leg. During the next few days severe headache, vomiting and edema of the legs and back were present. The time on the twenty-second day was forty minutes for the arm and ten minutes for the leg. The following day the output of urine was only 75 cc., the lowest at any time. The patient improved, the output of urine increased and the disappearance time rose gradually and reached normal on the thirty-third day of illness. There was still a trace of albumin, and a few casts and blood cells in the urine.

Another patient, aged four years, not tested at first, had blood cells in the urine and vomited on the twenty-fifth day of his illness,

when his disappearance time was fifty-five and fifty minutes for the arm and leg respectively. Two days later, with albumin, casts and blood in the urine, the time had fallen to thirty-three and thirty-seven minutes. The patient recovered very rapidly, with the disappearance time reaching fifty minutes on the thirty-first day. A child, aged seven years, with a mild course, had slight fever, with albumin, casts and blood in the urine, without edema or subjective symptoms on the nineteenth day. The disappearance time was thirty-five minutes for the arm and leg, whereas it had previously been forty and sixty minutes for the arm and leg respectively. On the thirty-first day the urine was normal and the time for the arm was sixty minutes. In 2 other instances mild nephritis, manifested only by traces of albumin and a few blood cells in the urine, without rise of temperature or symptoms, was not accompanied by reduction in the disappearance time.

Nine patients who were given scarlet fever antitoxin (at first that made by the Drs. Dick, later Squibb's preparation) were tested before, and again ten hours to two days after, injection. The increase of the disappearance time during the ten hour to two day periods immediately following the serum injections was not materially different from that seen during similar periods and day of disease in patients who did not get serum. About the same proportion of 14 patients who received antitoxin became normal within ten days as of those who did not receive antitoxin; but this represents a relatively more rapid improvement in the persons given antitoxin, since they as a group were much sicker.

Ten of the 14 patients given antitoxin had initial disappearance times, on either arm or leg, of thirty minutes or less. The test may be of help in deciding whether or not patients should be given antitoxin. Although the correspondence between the shortening of the disappearance time and the severity of the illness is not always exact, a time below thirty minutes may be considered as an indication for giving antitoxin.

Serum sickness with severe urticaria in 3 patients was accompanied by shortened disappearance time. In 1 the time dropped from forty-five to twenty-seven minutes with appearance of the urticaria, in another from sixty to thirty-five minutes and in the third it was twenty-four minutes at the onset of the urticaria.

The results of the tests on the arm and leg were approximately the same in the majority of instances. Where there was a discrepancy, disappearance from the leg was usually more rapid, possibly due to accompanying circulatory disturbance. For example, a patient who developed myocarditis in the second week had a disappearance time for the arm of fifty minutes and for the leg twenty-three minutes. A man who was on his feet and working through the first few days of illness, and had some edema of the legs, had an

arm time of sixty and a leg time of twenty-eight minutes on the fifth day. The urine was negative.

Summary. The time required for disappearance of the wheal made by injecting salt solution intradermally was found to be shortened in scarlet fever, with the amount of shortening roughly proportional to the severity of the illness. In the absence of complications the time returned to normal rapidly, usually before the patient was ready to be out of bed. Urticaria was associated with a shortened disappearance time. A disappearance time of less than thirty minutes may be taken as an additional indication, besides the patient's general condition, for giving scarlet fever antitoxin.

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HEMIHYPERTROPHY AND TWINNING.

A Further Study of the Nature of Hemihypertrophy with Report of a New Case.

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If it is in her moments of abnormality that Nature reveals her secrets, as Goethe once remarked, then the condition of hemihypertrophy assumes an added piquancy of interest. It is one of the rarest of medical anomalies and of such character that it might well disclose some glimpse of the inner mechanics of development.

It is essentially a developmental anomaly. It antedates birth and arises in some way as a partial deflection of the normal processes of growth. It strongly suggests a curtailed form of double mon-

FIG. 1.—Hemihypertrophic Case I (S. D.), aged thirteen years. (See Archives of Neurology and Psychiatry, 1921, **6**, 400.)

FIG. 3.—Palm prints of left and right hands of Case I. Showing disparity in size, but identity in the configuration of the friction ridges. The pattern formula for these ridges derived by Wilder's method is in each hand: 11 – 9 – 7 – $\bar{5}$ – C.

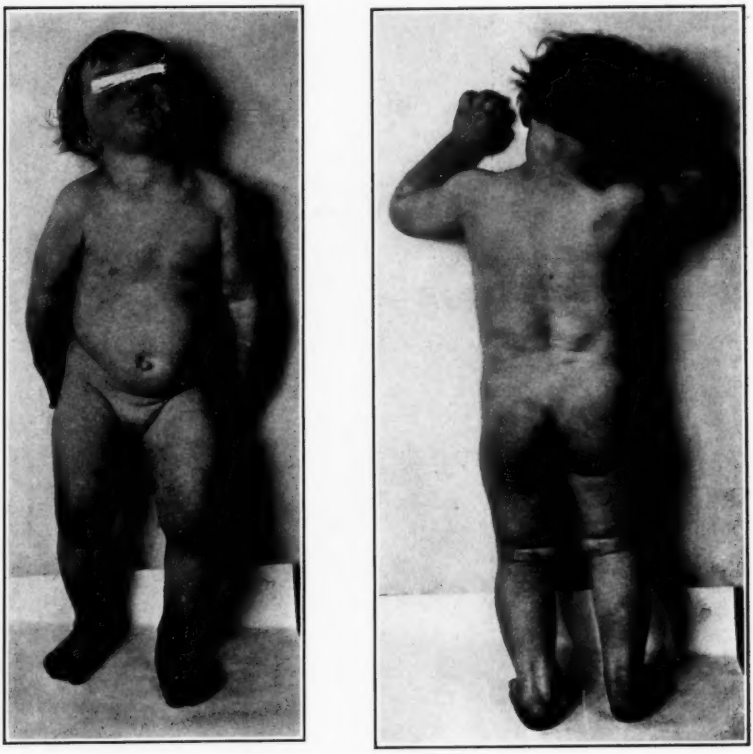

FIG. 4.—Hemihypertrophy, CASE II. Aged two years.

FIG. 5.—Roentgen ray of hands of CASE II. Aged two years.

strosity. It is a mild degree of gigantism, curiously confined to one side of the body. It is a unilateral enlargement of one-half of the soma, a hemimacrosomia. As such we may interpret the condition to be an atypical or a paradoxical form of twinning, a hybrid variant of the same process which may produce a double monster or a completely symmetrical individual. The biologic paradox consists in this, that the hemihypertrophy is neither double monstrosity nor bilateral duplicity; it is half of each, as though the individual remained two conjoined hemicreatures, each with a discrete though half realized genetic destiny.

In 1921, I reported a case of hemihypertrophy, associated with mental defect in a boy examined at thirteen years and again at twenty years of age. A few further observations on this youth reëxamined at the age of twenty-five years are reported below.

In view of the extreme rarity of well-defined hemihypertrophy, the laws of probability should scarcely permit another case to come unsought to our clinic. It was, therefore, a matter of great surprise to find the same condition repeated in a two-year-old girl who was referred to us on account of slowness and difficulty in walking. Perhaps the laws of chance were slightly weighted in our favor, because many of the children referred to the clinic are mentally deficient; and it was the thesis of our earlier paper that mental defect of some degree is found with disproportionate frequency in association with hemihypertrophy. It happens that in our second case this same association is repeated, confirming the suggestion previously made "that hemihypertrophy should be added to the list of developmental anomalies which bear some lawful relation to the incidence of mental deficiency."

Case Reports. CASE I.—S. D. male, examined at ages thirteen and twenty years, reëxamined at twenty-five years, has been under our observation for twelve years. (See Fig. 1.)

The subject was first examined when a boy aged thirteen years, and again at the age of twenty years. He presented a well-defined total unilateral hypertrophy of both soft and hard tissues on the right side, with characteristic port-wine telangiectatic patches of the skin, and definite mental defect.

The details of this case were reported in a previous article and need not be recapitulated. We recently renewed our acquaintance with this youth when he had reached the age of twenty-five years. This reëxamination furnished a few supplementary observations.

Physical remeasurements showed that there has been no change since the age of twenty. Height remains the same (67 inches). Length measures of arm, forearm and leg also remain as before. There has been a slight increase in weight, with associated increase in individual girth measures; but there has been no actual change in the degree of disparity. Morphologically, therefore, we may

conclude that in a period of twelve years the condition of hemihypertrophy has shown no progressive or equalizing tendency.

Psychologically, also the status of this case has remained remarkably constant. We made a rather detailed psychometric comparison of his mentality at the ages of twenty and twenty-five years, and found a thoroughgoing degree of correspondence in the behavior pictures of these two ages. The almost unmitigated lack of either deterioration or advance suggests that hemihypertrophy represents a well-ballasted deviation, in spite of the fact that differences of a physiologic character have been noted in the two sides.

At the age of thirteen years, S. D. had a mental age of four and a half years, yielding an intelligence quotient of thirty-five. Assuming that general mental maturity is attained or nearly attained at the

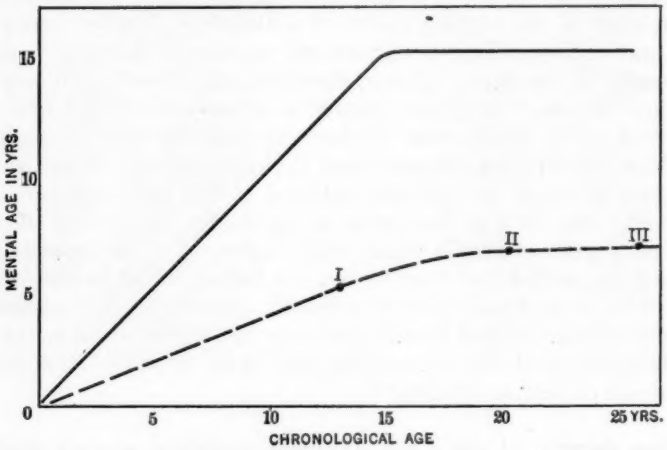

FIG. 2.—Mental growth chart of CASE I (S. D.).—The solid line shows the diagrammatic normal line of growth as measured by mental age. The broken line represents the approximate course of growth of S. D. as shown by mental-age ratings made when he was thirteen, twenty, and twenty-five years of age.

chronologic age of sixteen, he receives at the age of twenty-five, precisely the same mental rating, with a mental age of five years, eight months and an I. Q. of thirty-five. With a few minor exceptions there was virtual identity even in the individual test items of the examinations at twenty and at twenty-five years.

In 1921 he was asked: How many fingers have you on the right hand? On the left hand? On both hands? His answers were 7, 7, 8. In 1926, his answers were 7, 7, 14. In 1921, he spelled and misspelled as follows: *cat, house, it, Mew Haven, Spelling, Arithnetic.* In 1926 his orthography for these words was exactly the same, except that *it* was spelled *ta.*

Additional interesting details might be cited to show the permanence and completeness of the mental retardation, and the consis-

tency with which it has revealed itself in the past twelve years. The chart summarizes diagrammatically the character of this mental growth and subnormality. (See Fig. 2.)

Palm prints were made of the left and right hands of S. D. to determine whether there is any significant difference in the configuration of the friction ridges. These ridges appear as early as the fourth month of intrauterine life, and it seemed worth while to inquire whether the condition of hemihypertrophy had impressed any marked atypicality upon them. When mapped by Wilder's method, the ridges showed considerable identity of pattern. The pattern formula in each hand is 11–9–7–5–C. The only striking disparity is one of size. (See Fig. 3.)

CASE II.—M. S., female, was examined at ages two, three and four years. (See Fig. 4.)

Physical Development. This girl is a first child, with a negative family history, born normally (reported weight, 10 pounds). Was breast fed for eighteen months. No unusual illness known. One episode of convulsions, attributed to a digestive disturbance, reported at the age of two years. First tooth erupted at nine months. Walked at twenty months.

She walked with difficulty, frequently stumbling, and limping perceptibly. This was one reason why she was referred to our clinic. The limping proved to be due to the disproportionate length of the left leg. The disparity was sufficiently marked to cause the orthopedic clinic to recommend a built-up shoe for the right foot. Since then the motor difficulty has been largely overcome; but it caused much embarrassment in the early stages of walking.

Physical inspection as well as measurements showed that the asymmetry was of a total unilateral character, and that the whole left side was hypertrophied. Roentgen ray photographs showed that the bony as well as soft tissues were involved. The tongue was markedly hypertrophied to the left of the median line, and there was a definite corresponding convexity in the left lateral aspect of the tip. The tongue deviated to the right side on extrusion. (See Fig. 5.)

To ordinary inspection there was no difference in the teeth. There were eight on each side, with caries more advanced on the left side. The left half of the nose and the left nares were perceptibly larger.

The left half of the abdomen and the left labial fold were distinctly fuller. Palpation in the median line near the umbilicus showed *diastasis recti*, admitting the finger tips.

No areas of cutaneous congestion or deviations with regard to hair distribution were noted in the examination of the skin.

A tabulation of the significant measurements follows. These include comparative measurements of the bones, made directly from the Roentgen ray film.

Items.		Right.	Left.
Height	83 cm.		
Weight	14 kg.		
Cephalic girth	47 cm.		
" breadth	13 cm.		
" length	14.5 cm.		
Length of leg	.....	39.6 cm.	41.2 cm.
" femur (Roentgen ray)	.....	20	21
" tibia "	.....	16	16.5
" fibula "	.....	15	15.7
Thigh girth	.....	29	32
Calf girth	.....	21	22.2
Length of arm	.....	37.5	40
" humerus (Roentgen ray)	.....	13.2	15.2
" radius "	.....	11.2	11.5
Biceps girth	.....	18	19
Hand girth	.....	14	15
Length of foot	.....	12.4	13.4
Width of foot	.....	4.5	5.1
Length of ear	.....	5.7	6
Width of palpebral fissure	.....	0.8	1
Carpus Ossification Areas:			
Magnum	.....	7 x 8 mm.	5 x 7 mm.
Unciform	.....	6 x 8	5 x 8
Cuneiform	.....	4 x 5	3 x 4
Semilunar	.....	3 x 3	absent

Mental Development. A careful mental examination was made of this child when she was two and a quarter years of age and again when she was three years and four years of age. Her mental development has shown consistent retardation, though not on so low a level as the preceding case, S. D. The subnormality, however, justifies a diagnosis of mental defect of high grade.

On the first examination her chronologic age was two and a quarter years, her developmental level approximately eighteen months. At the chronologic age of three years her developmental level had reached two years. At the chronologic age of four it had reached approximately two and a half years. At each developmental examination, therefore, the developmental quotient (comparable to the I. Q.) was between sixty and sixty-five.

If, therefore, we plot the curve of mental growth diagrammatically as for the case of S. D., we obtain a similar picture of constancy in the subnormal rate of development. The accompanying psychograph (Fig. 6) summarizes the findings of the developmental examination. The developmental-age ratings were based on determinations of motor capacity, language, adaptive behavior and personal-social behavior, in accordance with the diagnostic procedures used at the Yale Psycho-Clinic in the examination of preschool children.

Hemihypertrophic Cases Reported in Literature to Date. Total Number 53. Although hemihypertrophy has been reported in the

medical literature of various countries for over a half century, a careful canvass of this literature netted a total of only 53 cases, including one kindly communicated to me by Dr. C. T. J. Dodge prior to publication. Thirteen of these cases have accrued since my previous tabulation made in 1921. I have merged all of these cases into one table, which is reproduced herewith.

The total figures show a slight preference for the female sex and for involvement of the right side. Eight cases or over 15 per cent are associated with mental subnormality. Almost half of the cases showed complicating skin lesions.

It is evident that hemihypertrophy is by no means an altogether benign anomaly, that it represents a disturbing deviation of the

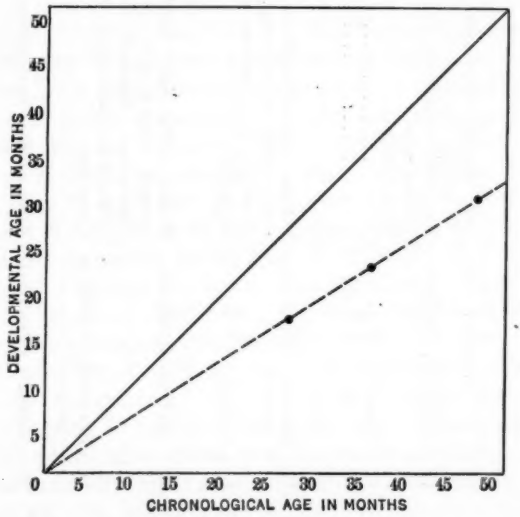

FIG. 6.—Mental-growth chart of CASE II (M. S.). The solid line shows the diagrammatic normal curve of growth. The broken line represents approximately the retarded course of growth of M. S., as shown by developmental-age ratings made when she was two years and three months, three years, and four years of age.

normal developmental complex. The nature of this disturbance may be considered by an analysis of what is known regarding the process of twinning.

Hemihypertrophy as a Phase of Twinning. Although considerable obscurity must attach to the origin of hemihypertrophy, the mode of its genesis may be eventually clarified by the researches of experimental biology. Many of these researches naturally bear on problems of symmetry, dichotomy, and growth regulation.

In earlier papers, we have suggested that human hemihypertrophy can be conceived as an imbalance of the normal process of twinning which underlies all bilateral structures. From this point of view,

Author.	Sex.	Age.	Side.	Mentality.	Skin complications.	Special features.
Bousquet, M. Pierre, 1921 .	F.	4 mos.	R	Undetermined	None	Lateral deviation of right phalanges.
Hall, Geo. E., 1921 . . .	F.	7 mos.	R	.....	Without a blemish	Lips, ear, tongue, cheek asymmetric. Nipples, mammæ, scapula and clavicles equal. Cranium symmetrical. May involve only soft parts. May be false type.
Babonneix et Buizard, 1922	M.	4½ mos.	R	.....	Very extensive nevi particularly of left leg	Marked transverse nasal vein.
Vonderweidt, Dr., 1922 .	M.	11½ mos.	R	(Dentition delayed)	Right side more congested when infant cries	Asymmetry more pronounced in lower extremities.
Cozzolino, O., 1923 . . .	M.	6½ mos.	L	.....	None—clear	
Paterson and Reynolds, 1923	F.	6 mos.	L	Seemed normal	.....	Skull symmetrical.
Paterson and Reynolds, 1923	F.	13 yrs.	R	.....	.....	Involves face only, right permanent, upper molar enlarged and left missing.
Reed, A. C., 1923 . . .	F.	15½ yrs.	R	Normal, bright demeanor	Diffuse areas of passive congestion mostly on right leg, thigh buttocks and lumbar region	Right breast larger—more pendulous.
Stanton, J. N. and Tuft, Louis, 1923	F.	16 yrs.	L	Normal	Negative	Asymmetry of tongue caused difficulty in *th* sound and in swallowing.
Lisser, Hans, 1924 . . .	F.	45 yrs.	R	Nervous, depressed	Finger nails, right hand dry, rough, ridged (left, smooth, glistening). Mustache fuller on right side. hair coarse, dry.	Tongue, lip, and right pupil all larger on right side.
Mohr, Geo. J., 1925 . .	F.	9 mos.	L	Retarded; unable to sit alone	Clear, dry	Tongue protrudes and is asymmetric. Thyroid deficiency suggested.
Dodge, C. T. J., unpublished, 1926	M.	3½ yrs.	R	Mentally subnormal	A museum of nevi lipomata	Macrodactyly. Deformity of left knee. Varicose veins.
Gesell, A., (present publication), 1926	F.	18 mos.	L	Mentally subnormal	None	Left side relatively immobile in smiling.
Gesell, A. Totals of 40 previous cases, tabulated in 1921, Arch. Neur. and Psychiatry, vol. vi, pp. 400	19 M. 21 F.	.....	13 L. 27 R.	5 cases mentally subnormal	19 cases with skin complications	Varied (see table).
Grand total	23 M. 30 F.	.....	35 R 28 L	8 mentally subnormal,	24 cases with skin complications	

hemihypertrophy is an epigenetic deviation rather than a germinal deformity. It represents some defect of the inner organismic regulation, or some disparity in the intimate environmental factors exerted in the early stages of cleavage. It is, accordingly, not an altogether unique anomaly but may be brought into the category of twinning and of double monstrosity.

Bateson has given us a very broad conception of twinning in his formula "the production of equivalent structures by division." He regards it as a fundamental manifestation of life. "When I look at a dividing cell, I feel as an astronomer might do if he beheld the formation of a double star; that an original act of Nature was taking place before me." Cellular division, as such, is not twinning; but the tendency of the divided or repeated parts to assume symmetrical relations may be so regarded; and this tendency is an almost universal feature of biologic mechanics. The fact that the experimental embryologist can bring about the growth of a paired structure by a simple wound of a single limb bud reveals the fundamental nature of twinning. Of similar significance is the fact that Loeb produced a 90 per cent increase in twins by a simple immersion of his experimental eggs in lime-free sea water, which caused the segments of the living eggs to fall apart as they were formed. Newman, likewise, regards the phenomenon of twinning as a "very fundamental process almost universal in the field of biology. For wherever we have bilateral doubling, we have twinning in some form."

From this point of view every bilateral individual may almost be considered as being morphologically a pair of twins. This view is so legitimate that it need not be called paradoxical. The human individual is undoubtedly derived from a single fertilized cell. He is monozygotic in origin. From this zygote, through a process of symmetrical division, develop all his right and left hand homologous organs and the right and left halves of his "unpaired" organs and structures. He is a product of developmental duplicity. Now in the case of true, complete monozygotic twins, this process of duplication has been carried to such a degree that two offspring result from the single ovum. A perfectly symmetrical bilateral individual on the one hand, and a perfect pair of duplicated individuals on the other represent the ideal extremes of the process of twinning. Between these extremes there are many gradations and deviations, some of them benign others monstrous, in character. Instead of a full twinning of the whole body, there may be twinning of various parts or only of one part. For example in the type of twinship known as *diprosopus diopthalmus*, described by Ballantyne, "the size of the head and the presence of two noses may be almost the only signs of duplicity."

The studies of Stockard and of Wilder have concretely shown the close genetic relationships between monozygotic twinning and double monstrosity. Stockard has also experimentally produced in the

Grand total . . . . . { 23 M. / 30 F. } ..... { 35 R / 28 L } 8 mentally subnormal, 24 cases with skin complications

trout and in the sea minnow unilateral deformities of development which resembled hemihypertrophy. He was able to arrange specimens of his experimental fish in graded series, demonstrating "a continuity of the series from *monstra in defectu* through the simple normal individuals to *monstra in excessu* and finally identical twins."

Stockard holds that the specific rate of development in any animal is probably dependent upon the rate of oxidation in the protoplasm of the species. Experimentally, therefore, the rate of development may be retarded by lowering the surrounding temperature, which reduces the rate of oxidation. Stockard found that "practically any deformity recorded in the literature other than those resulting from germinal variations or mutations may be induced by lowering the temperature and thus modifying the developmental rate."

The exact manner in which these developmental deviations are accomplished, is differently interpreted by different biologists. The tendency of recent research is to stress not the inherent molecular constitution of the germ, but the reaction of the specific growing protoplasm to the immediate environmental conditions. R. S. Lillie has suggested that the process of development is basically regulated by some physiologic influence of a repressive or inhibitory kind comparable to chemical-distance-action, which is indeed essentially a form of bioelectric control through potential difference. C. N. Child has elaborated the concept of the physiologic gradient.

This concept affords some clue to the mechanism of hemihypertrophy, or at least to its rationalization. Child asserts that at present there is "no evidence to indicate that axiate pattern can arise in any other way than as a gradient in a physiologic state." Polarity and symmetry therefore are dependent primarily upon "quantitative dynamic gradients in living protoplasms," whose existence Child has experimentally demonstrated in numerous ways. Accordingly, "physiologic dominance" and "physiologic isolation," and the relations between them are the dynamic factors which determine form regulation, symmetry, and frequently duplication and reduplication. Or one dominant region, because of its shape, may split into two regions of physiologic dominance, which will result in a greater or less degree of twinning. The range of dominance also plays a role in determining the limit of individual size. Since the concepts of gradient, dominancy, and isolation are essentially quantitative, it follows that a slight quantitative imbalance in the early stages of embryonic cleavage, might project itself into the whole-growth cycle as either a partial, or a total unilateral asymmetry.

Although one speaks of total hemihypertrophy as though it were a defined clinical entity it should be emphasized that even among the relatively small number of cases recorded in the literature, there is an impressive range of variation. One case will show a few nevi, another extensive nevi, another will report the skin to be entirely normal. In some cases the vascular complications are conspicuous,

in others wanting. The fact that hemihypertrophy is associated with both normal and defective mentality also is noteworthy.

Does not this variability in associated symptoms suggest that the condition arises out of environmental or epigenetic conditions? Growth is constantly regulated by interacting factors, and the specific structural features of any given case of hemihypertrophy will depend upon the precise moment at which the disturbing influence began to operate. The severity of the cerebral arrest, for example, will depend upon the dominance or the developmental stage of the neurogenic portions of the embryo. We are thinking here of subtle inhibitions or arrests of growth in the morphogenetic interplay of various organ systems, or even in the several components of a complicated system like the cerebrum. If grosser teratologic suppressions occur, subtler alterations are theoretically even more certain. On the grosser scale, Stockard, for example, found that the initial growth which gives origin to an embryonic system such as the brain and spinal cord "is linear in type, until a definite length is attained when linear growth subsides. This is followed by a series of lateral outgrowths in consecutive fashion. These lateral outgrowths from the central nervous system may be experimentally suppressed by slowing development at definite times . . ." The constantly changing status of the embryonic organs and the sensitiveness of the dynamic equilibrium which prevails furnish an ample basis for variable peculiarities in the pathologic picture of hemihypertrophy.

There can be little doubt that in some instances there is more than a morphologic difference between the opposite sides of the body. There is a perceptible physiologic or energetic difference, which heightens the temperature of the affected side, accelerates the growth of the nails and hair, and even hastens the eruption of the teeth on that side. Thus in one instance the developmental disparity was so great that there were eight teeth on the hypertrophic side with none erupted on the normal side.

This amazing discrepancy obliges us to recognize an energetic difference. It means that sometimes an individual may have two physiologic ages at the same time, one for each half of a developmentally asymmetric body. It also suggests that in some of these cases the physical signs of senility might be detected earlier on one side than on the other. This is another striking indication of the twoness of the hemihypertrophic individual.

Wilder has studied the genetic relationships between monozygotic twinning and double monsters (diplopagi). A gradation of the interrelations of various sorts of diplopagi and duplicate twins is diagrammatically pictured in the accompanying figure (Fig. 7). This diagram does not exhaust all of the possibilities, and does not aim to include those instances where one twin is included by the other, or where one twin becomes a mere parasite upon its normal co-twin. Incidentally, it may be recalled that such a parasite may degenerate

into an acephalic, acardiac, trunkless or amorphous mass. Here, as Ballantyne remarks, Nature "attains to the extreme limit of teratologic expression."

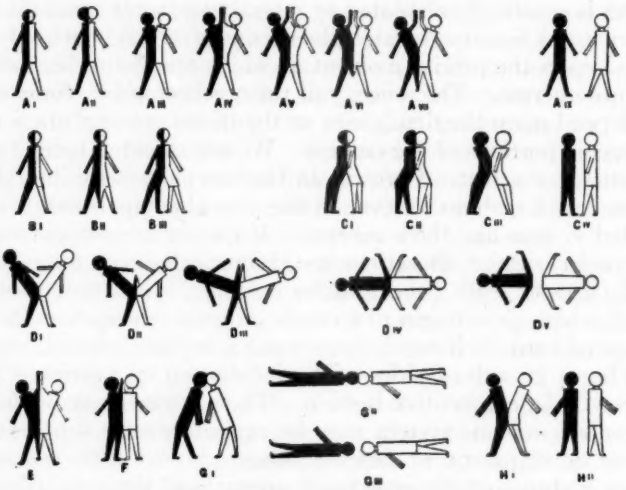

FIG. 7.—Wilder's diagrams showing the interrelations of various sorts of diplopagi and duplicate twins. (From American Journal of Anatomy, 3, 473.)

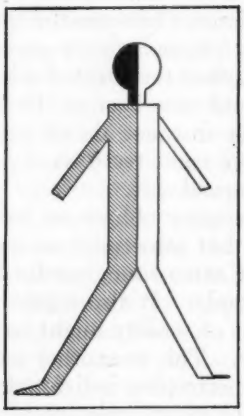

FIG. 8.—Diagram suggesting hemihypertrophy as a variant between AI and AII in the above series. (Fig. 7.)

Twinning, therefore, is a highly variable process which expresses itself on an enormously wide gamut. It may produce perfect symmetry and mirror imagery; or it may produce gross disparity. Nowhere in the study of man do we find such complete duplication

of individuality as among monozygotic twins; and nowhere do we find also such profound and monstrous degrees of individual difference as among twins derived from the selfsame egg. By the same token we may expect to find mild degrees of monstrosity or of incipient monstrosity such as hemihypertrophy embodies. We might then add to Wilder's diagrams a silhouette of an individual whose morphologic eccentricity is indicated by a larger and a lesser half. (See Fig. 8.)

H. H. Newman has made extensive studies of twinning in the armadillo. This work formed the basis of his volume on *The Biology of Twins*. More recently he has made an experimental analysis of twinning in the Pacific Coast starfish, and written an additional volume entitled *The Physiology of Twinning*. This volume contains material of medical interest—a chapter on the developmental hazards of human twins, and a chapter on hemihypertrophy. In many respects Newman's interpretations are in harmony with those already referred to. He believes that "twinning is essentially a phenomenon involving a physiologic isolation of equivalent parts of the blastoderm." The cause of the isolation is a temporary cessation or retardation of development at a critical period.

In his discussion of hemihypertrophy he suggests that the condition may be "due to a physical inequality of the two bilateral primordia so that one side would be more affected by subnormal conditions than the other . . . Even with this possible explanation of asymmetry in mind I find myself in essential agreement with Dr. Gesell in his interpretation of hemihypertrophy as a minimal phase of double monstrosity. We may conclude that, since twinning in general consists of a more or less complete isolation, physiologic at first and later physical, of the bilateral primordia of a single embryonic axis, there may readily occur slight degrees of physiologic isolation or independence of the two halves of the body. Hemihypertrophy, complete and incomplete, would then be the result of some deficiency confined to one side, and the associated peculiarities would be viewed as secondary consequences of the primary deficiency."

One of these possible secondary consequences is mental defect. Although it is not an inevitable consequence it is sufficiently frequent to be significant. It suggests that an abnormality in the process of bilateral doubling may involve important disturbances of normal tissue development of the individual. Total hemihypertrophy, itself, is a rare phenomenon; but there may well be numerous instances of concealed or unrecognized asymmetry which bear a comparable relation to the production of mental deficiency. Probably a considerable proportion of congenital cases of mental deficiency may be attributed to epigenetic factors similar to those discussed in connection with hemihypertrophy. It is in this sense

that the study of twinning reveals new fields for the discovery of the causes of developmental defect.

Summary. 1. The medical literature on hemihypertrophy is reviewed and brought to date. Forty cases of the total unilateral type were tabulated by the author in 1921. Since then 13 additional cases have accrued. Of the combined number of 53 cases, 23 are male, 30 female. The right side was affected in 35, the left in 28. Skin complications were present in 24 instances. Mental subnormality was found in 8 instances.

2. The author reports a second case associated with mental defect. The subject is a girl examined at two, three and four years of age. The mental and physical measurements indicate that the condition has remained relatively constant. Remeasurements of the author's earlier case showed the same constancy in both its mental and physical features.

3. Hemihypertrophy is interpreted as a minimal form of twinning. Its genetic relation to the normal process of bilateral doubling and of double monstrosity is indicated. Recent researches in the field of experimental biology are cited, notably those of Stockard, Wilder and Newman.

4. The significance of the physiologic gradient, of physiologic isolation and of the partial retardation of developmental rate is considered in the pathogenesis of hemihypertrophy.

5. The relatively high incidence of mental defect is considered significant. The proportion of mentally subnormal cases would probably be still higher if mental examinations had been made and if some of the subjects had been more advanced in age. The mental defect is attributed to a disturbance of normal tissue development associated with an imbalance of the embryonic process of twinning.

6. Deviations or imperfections in twinning may play a very influential role in the production of developmental defect, though the details of the mechanism are not understood. Further biometric and clinical studies in asymmetry are therefore of medical importance.

The bibliography below is supplementary to a more extended one published in 1921 with the author's article in *Archives of Neurology and Psychiatry* (vol. 6).

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THE ELECTROCARDIOGRAM IN BRONCHIAL ASTHMA.

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The compensatory capacity of muscular structures in the body is biologically interesting. The response of the muscle cavities to obstacles to their proper contraction is particularly exemplified by hypertrophy of the musculature of the left ventricle of the heart in hypertension.

In the present study, we analyze the electrocardiograms of a series of cases in an endeavor to ascertain the effects of chronic emphysema and bronchial asthma upon the right ventricle.

The Electrocardiogram in Cardiac Hypertrophy.—It is important to distinguish the mass of right heart musculature from that of the left ventricle. Thus there are two main divisions of the mass of heart muscle tissue: (1) The vortex fibers arising along the entire

circumference of the coronary sulcus and spreading over the entire surface of both ventricles to turn in at the apex and form the inner layer of muscle of the left ventricle; (2) the main mass of muscle of the wall of the right ventricle.[1] This anatomic distinction implies also a physiologic one for each of the heart chambers.

It has been shown by Einthoven,[2] Müller,[3] Lewis and Guilder,[4] and others[5] that certain clinical valvular conditions cause more or less typical changes in the electrocardiogram corresponding to the preponderating hypertrophy of one or the other chamber of the heart. Although there may be other factors influencing the form of the electrocardiogram,[6] preponderance of one or the other ventricle shown in the electrocardiogram may be taken as an index of relative hypertrophy.

The normal *Q-R-S* group is produced by the algebraic summation of the left ventricular electrocardiogram (levocardiogram) and the right ventricular electrocardiogram (dextrocardiogram). In the normal electrocardiogram, the effects of the two ventricles, in spite of the greater mass of the left, are fairly well balanced, producing the normal *Q-R-S* curve. A relative increase in the mass of the one or the other chamber alters the balance between right and left ventricular effects.

When the heart is greatly hypertrophied, preponderance of one side or the other is the main factor influencing the ventricular complex of the electrocardiogram. Variations in the position of the heart is another important factor. It has been shown that the relative dilatation of the two chambers, on the contrary, plays no appreciable part in determining the form of the ventricular complex. Prominent Q_3 and S_1 in the electrocardiogram are right ventricular effects. R_3 is chiefly a right ventricular effect. The tall R_3 and deep S_1 of right ventricular hypertrophy are the expression of preponderance of the dextrocardiogram.

Lewis concluded that the physical signs which are customarily employed at the bedside to differentiate left from right ventricular hypertrophy have little or no real value as checked by postmortem observations. In studying hypertrophy, even inspection of the exposed heart is quite insufficient, and a method of weighing the muscles of the separate chambers is alone reliable.[4]

The electrocardiographic curves, on the contrary, appeared in harmony with our knowledge of hypertrophy in various forms of valvular conditions. The view that hypertrophy is secondary to increased work, and that such hypertrophy is manifested by those heart chambers upon which the increased burden falls, is paramount today. The theory finds full support in clinical observations upon mitral stenosis. High blood pressure and aortic disease appear to be especially potent in creating a preponderance of the left ventricle. The commonest type of hypertrophy, however, is a uniform hypertrophy. In renal disease this is the rule.

The characteristics of the electrocardiogram have not been previously investigated in relation to bronchial asthma.

The Pulmonary Circulation and the Heart. It has long been recognized that a mechanical relationship exists between the pulmonary circulation and the condition of the right side of the heart. Clinically, it is known that prolonged pulmonary stasis and increased pressure in the pulmonary circulation result in right heart enlargement. In mitral stenosis or where pulmonary resistance increases, the initial tension of the right ventricle increases with the pressure in the pulmonary vessels; hypertrophy then follows. This sequence of events is rational and easily understood. In cases of hypertension, there is often hypertrophy of both the left and right ventricles. This is because the right side acts as an auxiliary pump to maintain a greater initial tension in the left ventricle.

In cases of destruction of part of the lung tissue such as takes place in pulmonary tuberculosis, there develops a compensatory dilatation of other capillaries. This accounts for the observation that right ventricular predominance is not found more frequently in association with fibroid phthisis, or with pleural adhesion than with other types of pulmonary fibrosis.[7] The same holds true when, experimentally, one or more of the pulmonary veins are tied off.[8] In these cases, it is found that there is none or only very slight increase of pressure in the remaining pulmonary veins, due of course to compensatory dilatation of the remaining vascular field. Clinically, the interesting observation may be made that the pulmonic second sound does not become accentuated in cases of postoperative pulmonary embolism, and I have observed it in a number of cases. This indicates that there in no increase of pressure in the pulmonary artery after pulmonary embolism, due to the compensatory dilatation of the nonoccluded vessels.

The effect that this compensatory process will have on the right ventricle varies with the extent of the narrowing of the stream bed of the lungs. At first, the dilatation of the arterioles will offset the narrowed blood bed, but with more extensive obstruction of the pulmonary vessels, the right ventricle will be called on for more work to maintain the minute volume flow in the lungs, and will dilate and eventually hypertrophy. This has been shown experimentally.[9]

Respiration and Pulmonary Circulation. With each inspiratory spreading of the chest, in normal respiration, the negative intrathoracic pressure increases. All the tissues in the thorax come into a state of elastic tension, the walls of the heart and the great vessels partaking in this. Inspiration, therefore, produces suction of blood from the periphery into the large veins and into the right heart. The pressure in the pulmonary capillaries increases as the air vesicles distend with inspiration, forcing the blood through the pulmonary veins into the left heart.

In asthma, the defective respiration is characterized especially

by expiratory dyspnea, producing increased intravesicular tension in the lung. This is the prominent functional factor in the production of pulmonary emphysema. Most asthmatics, therefore, develop emphysema to a decided degree. Again, the expiratory dyspnea and increased intravesicular tension of air in the lungs have a direct effect upon increasing the blood pressure in the pulmonary artery and thus can be assumed to have an effect on the right heart. That is, the strain upon the heart is probably largely due to increase of pressure in the pulmonary circuit during forced expiration.[10]

A lesser factor tending to produce right heart hypertrophy is the nasal obstruction occasionally present in cases of bronchial asthma.[11]

Studies on patients suffering from chronic emphysema and bronchial asthma showed that the total lung volume remains about the same, but the vital capacity is much diminished and the residual air very much increased, indicating a compressed and narrowed capillary field in the lungs.[12]

Emphysema and Cardiac Hypertrophy. — Emphysema accompanies long-standing asthma. With that, of course, pathologically there is marked thinning of the vesicular walls and consequent narrowing of the vessels and capillaries. Occasionally, these become occluded and even torn through.[13] This series of events tends to occur in most cases of bronchial asthma—in the long standing and intractable cases more than in those of short duration. The capillary field is thus lessened without the possibility of a compensatory dilatation. As a result there is dilatation and atherosclerosis of the pulmonary artery and dilatation and hypertrophy of the right ventricle, as it is called upon to force the same amount of blood as before through the narrowed capillary field of the entire lung. Finally this may even lead to cardiac insufficiency.

Clinical Comments. The clinical recognition of right ventricular hypertrophy in bronchial asthma is not emphasized in most studies of the subject. With reference to emphysema, von Leube states in the differentiation from cardiac asthma that a "dilatation affecting essentially only the right heart points to a spasmodic asthma."[14]

As noted above, the experimental method of occluding the pulmonary circulation or increasing the pulmonary resistance in other ways thereby to produce effects on the heart, is not helpful in the study of bronchial asthma.

The marked encroachment of the lung volume upon its capillary capacity together with the varying intrathoracic pressure constitutes a decided strain upon the right ventricle, to which the organ responds by hypertrophy. Enlargement of the right heart is usually found in advanced emphysema, unless masked by the physical signs of the emphysematous lung.

The analysis of Roentgen ray and electrocardiographic findings in pronounced cases of bronchial asthma of long duration is of

assistance in diagnosis. We have not included roentgenographic analyses in this study. The electrocardiogram is especially helpful in showing the relative preponderance of one side of the heart over the other.

The association of complicating clinical features such as arterial hypertension producing left ventricular preponderance makes it important to analyze the cases in detail. The record of the blood pressure is one important index and the amount of emphysema is, of course, the other. The cases are tabulated to show these and other relevant clinical findings such as duration of the disease and severity of the attacks. The duration and severity I have grouped together as we aim to discover the summation of the effects of asthma. The cases are also classified in groups according to age and the diastolic blood-pressure findings. I consider the diastolic reading, as it is more constant, more important than the systolic in the analysis of blood-pressure studies.

Analysis of Electrocardiographic Records. The electrocardiograms were reported in the usual routine manner with an endeavor to commit ourselves to an opinion of right preponderance when such a tendency was indicated by a combination of deep S_1 with low R_3, or with prominent Q_3. On the other hand, left preponderance was indicated by deep S_3 and high R_1.

Four predominating characteristics were found in the analysis of the electrocardiograms of these cases: (1) Left ventricular preponderance; (2) right ventricular preponderance; (3) high P (auricular) wave in Leads II and III; (5) T wave inverted in Lead III.

Other conditions being equal, left ventricular preponderance is an almost constant association of high blood pressure (Table I).

TABLE I.—CLASSIFICATION OF ELECTROCARDIOGRAPHIC CHANGES ACCORDING TO DIASTOLIC BLOOD PRESSURE.

Diastolic blood-pressure.	No. cases.	No preponderance.		R. V. P.		L. V. P.		T_3 inverted.	
		No.	%.	No.	%.	No.	%.	No.	%.
Under 70 mm. Hg	9	4	44	4	44	1	11	2	22
70 to 79 mm. Hg	14	7	50	2	14	5	35	3	21
80 to 89 mm. Hg	11	6	54	1	9	4	36	2	18
90 to 99 mm. Hg	8	1	12	2	25	5	62	2	25
100 and over mm. Hg	8	1	12	1	12	6	75	1	25
Totals	50	19		10		21		10	

When in a case of hypertension, therefore, there is no ventricular preponderance, we may assume the coëxistence of right heart hypertrophy. In cases of emphysema and asthma, we must assume this

on the basis of pulmonary stasis. Of the 21 cases of left ventricular preponderance, the largest number showed hypertension. It is seen that the higher the diastolic pressure, the greater is the proportion of cases showing left ventricular preponderance. It is noted that in a number of our cases, even with high blood pressure, there is no left ventricular preponderance. That is, the normal balance between the musculature of the two ventricles is maintained. This implies and indicates right ventricular hypertrophy. The majority of cases showing left ventricular preponderance are above the age of forty years or with a diastolic pressure above 90 (Table II).

TABLE II.—CLASSIFICATION OF ELECTROCARDIOGRAPHIC CHANGES ACCORDING TO AGE.

Age.	Number.	No preponderance.	R. V. P.	L. V. P.	T_3 inverted.	P_3 and P_4 high.
Under 20	6	3	3	0	1	1
20 to 29	9	4	4	1	1	2
30 to 39	6	4	1	2	1	
40 to 49	18	6	1	10	4	
50 and over	11	2	1	8	3	1

Thus it is evident that the superposition of the effect of left ventricular preponderance on a preëxisting right ventricular preponderance masks the hypertrophy of the right ventricle in these casesof asthma. It is probable and it may be assumed that a certain amount of right ventricular hypertrophy is masked by the predominating hypertrophy of the left ventricle.

It is seen from the table that of the 50 cases 10 showed right ventricular preponderance. This does not present the full number in which right hypertrophy took place. Although not tabulated, in this group may properly be included the cases showing no preponderance but showing hypertension or some other factor which counterbalanced the effect of asthma. It becomes apparent that the electrocardiogram must be considered in conjunction with all the other clinical aspects of cases in order that it may be correctly interpreted.

The frequent association of the high *P* wave with right ventricular preponderance suggests that this is another evidence of the effect of pulmonary stasis on the right heart. Since the effect is first upon the ventricle and only secondarily upon the auricles, a high *P* wave would theoretically not be found in association with left ventricular preponderance except in cases of mitral stenosis. This assumption is supported by the analysis of our tables. It is a surprising finding that the 4 cases showing a high *P* wave in Leads II and III occur in cases in which there is right ventricular preponderance (Table III).

TABLE III.—RELATION OF HIGH P WAVE IN LEADS II AND III TO VENTRICULAR PREPONDERANCE.

Name.	Sex.	Age.	Diastolic pressure.	Preponderance.
I. F.	M.	26	60	R. V. P.
L. G.	F.	21	74	R. V. P.
A. E.	F.	50	94	R. V. P.
M. L.	M.	11	Low	R. V. P.

The inversion of the T wave in Lead III showed no particular relation to the ventricular predominance (Table IV). Three of the inverted T_3 electrocardiograms showed no predominance;

TABLE IV.—RELATION OF INVERSION OF THE T WAVE IN LEAD III TO VENTRICULAR PREPONDERANCE AND SYSTOLIC PRESSURE.

	Number of cases.	Systolic pressures.
T_3 inverted with no ventricular preponderance	3	124
		100
		114
T_3 inverted with right ventricular preponderance	3	96
		146
		137
T_3 inverted with left ventricular preponderance	4	114
		100
		140
Total T_3 inversion cases	10	

TABLE V.—RELATION OF RIGHT VENTRICULAR PREPONDERANCE TO AGE AND BLOOD PRESSURE.

Name.	Sex.	Age.	Systolic pressure.	Diastolic pressure.
A. E.	F.	50	160	94
I. F.	M.	26	96	60
B. F.	F.	40	137	78
L. G.	F.	21	100	74
F. K.	F.	37	122	88
M. L.	M.	11	90	
M. M.	M.	12	90	
W. M.	M.	7	96	64
M. R.	F.	23	128	98
E. S.	F.	29	146	106

three showed right predominance and four showed left ventricular predominance. It is usually held that the inversion of the T wave bears a relation to hypertension. It does not seem to be the case in this group. As noticed from the table, the blood pressures are at various levels in these cases. Although T_3 inversion has no apparent relation to the blood pressure, it occurs in cases above the age of forty years, which suggests that it may be an evidence of myocardial changes associated with advancing age.

Conclusions. 1. Of 50 cases of bronchial asthma and emphysema, 10 (20 per cent) showed electrocardiographic evidence of right ventricular preponderance.

2. The remaining cases showed electrocardiographically no preponderance and left ventricular preponderance in about equal number. Among these, a large proportion of cases showed hypertension and aortic atheroma; factors which influenced the hypertrophy of the left ventricle to a degree sufficient to mask the electrocardiographic evidence of right ventricular hypertrophy.

3. Four of the cases showing right ventricular preponderance also showed high P_2 and P_3.

4. Inversion of the T wave in Lead III showed no particular relation to the ventricular predominance.

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FACTORS OF A GROWTH REGULATORY NATURE IN TISSUE CELLS.*

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The tissue culture method has rendered it possible to undertake accurate analyses of the cell nutrition and the interaction of the different cell types. It is possible to cultivate pure strains of cells with a known activity in a culture medium of invariable composition over long periods of time.

It is known from the investigation of Carrel that the growth of tissue cells is dependent upon the concentration in the pericellular

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fluid of substances from which the cells are able to synthetize their own cytoplasm, and of certain hormones. The growth-promoting substances, products of embryonic tissues and leukocytes, as taken up by the cells from the humors of the body, have been termed "trephones" by Carrel.

Experimental facts which shall be reported here lead us to assume the existence of certain growth principles besides the trephones, namely, those which circulate in the living protoplasm only. In other words, we are forced to conceive the existence of a hitherto disregarded circulatory system in the body, that is, a system, which probably is a kind of mutual exchange of protoplasm between the cells. These principles I have termed "desmones" (from δεσμός, a strap or string), and this name is used as a collective term for principles circulating in the protoplasm from cell to cell through the fine anastomoses, and mutually controlling the growth and proliferation of tissue cells.

Some years ago I reported experiments which showed that single isolated tissue cells *in vitro* were not able to divide and regenerate to form a cell colony. The cells lived and moved about, but were incapable of multiplying. When a certain number of cells were in protoplasmic interconnection, however, they were able to multiply.

It is well known that the intercellular connections of the tissue cells serve as pathways for the conveyance of stimuli of various kinds. When two pieces of pulsating heart were brought close together *in vitro*, the two pieces pulsating in different rhythms, I found that it was possible to obtain a physiological unit, a simultaneous contraction of the two pieces, when the contractile elements of the one piece of heart grew in protoplasmic contact with that of the other piece. A simultaneous contraction of the two pieces did not take place when a layer of fibroblasts was interposed between the two bits of heart; nor was simultaneous contraction obtained when the two pieces of heart belonged to two different species (duck and chicken). These facts seem to prove that the stimuli leading to contraction of the myoblasts are rather specific to species of cells and species of animal.

When cultivating tissue cells *in vitro* it will be found that for some reason or other the cells occasionally begin to grow badly and nearly die. Instead of a regular dense mass of tissue cells the culture is transformed so as to consist of cells arranged in irregular chains or in an open meshwork. It was evident that lack of trephones was not the cause of degeneration of the cells, because the culture medium contained plenty of freshly prepared embryonic tissue juice; nevertheless it was incapable of promoting the growth of fibroblasts. When a very minute piece of a fibroblast culture was brought in direct connection with the dying culture of cells a rejuvenation of the culture took place, that is, the degenerated fibroblasts now assumed the aspect of young cells in active condition

and began to proliferate vigorously. The rejuvenation of the cells directly opposite the added piece of fibroblast culture was very striking, even within a short time. The rejuvenation is probably due to the fact that a something is brought into the dying cells which hitherto has been missing.

When small quantities of leukocytes were added to a culture of dying fibroblasts this resulted also in a rejuvenation of the cells. It was observed that leukocytes form "provisional" anastomoses with the fibroblasts, and thus in this way may convey a something to the degenerated cells which causes rejuvenation.

When cultivating chicken sarcoma I have often noticed cultures that are growing badly. It has been possible to save cultures of almost dying sarcoma cells by adding pieces of normal growing cultures of fibroblasts. Even when cultures of the sarcoma cells looked hopeless, and only a few extremely degenerated cells were left, such cultures could be successfully rejuvenated by adding a piece of fibroblastic tissue.

As already mentioned, it was not possible to establish a physiological unit of two pieces of pulsating heart tissue belonging to two different species, nor was it possible to obtain a physiologic unit of two pulsating pieces of heart when a layer of fibroblasts was interposed. It was further observed that the growth of pure epithelium was not promoted by addition of fibroblastic tissue to it or *vice versa*, and an amalgamation of the two-cell types was not found to take place. The individual epithelial cells grew in solid contact with each other surrounded by fibroblasts. This fact shows also that the principles controlling the growth and multiplication of normal epithelium cannot be utilized by normal connective-tissue cells or *vice versa*. In contrast with the trephones, the desmones are specific.

If a few sarcoma cells are added to a culture of epithelium an amalgamation takes place immediately. A capital biologic difference between a normal and a malignant tissue cell is therefore this: The malignant cell is capable of utilizing the specific desmones, or growth principles, of all the various cell types in the organism, whereas an epithelial cell can utilize only the desmones of epithelial cells and fibroblasts only those of the fibroblasts. The explanation might, however, be that the malignant tissue cell is able to build up the growth principles, independent of the relation to other cell individuals.

We can summarize the result of our investigation by saying that the growth and proliferation of tissue cells depend upon the concentration in the pericellular fluid of certain food substances, the trephones of Carrel, and of hormones. Besides these external, nonspecific growth principles we may now add certain internal, specific principles, the desmones, which rule coördinate growth of tissue cells and which are found to exist only in the living protoplasm of the cells.

We have learned from our experiments that the external growth principles alone are not sufficient to support the life and function of the tissue cells. Even under conditions where an abundance of trephones and hormones are to be found, isolated tissue cells are incapable of multiplying. How the phenomenon may be interpreted is not easy to say. We are justified in assuming from our experimental knowledge only the existence of such growth principles and correlation principles as mentioned.

Consideration of these principles seems to explain many physiologic cell processes.

The extent to which the desmones are specific we do not yet know; but there is every reason to believe that the healing of grafts mainly depends upon the possibilities of the grafted cells being in harmony with the cells of the host, that is, upon whether the grafted cells are capable of utilizing the desmones of the cells from the host or not. Even if the humors of the body are in no way antagonistic to the grafted cells, they will die if they are not able to accomplish an exchange of desmones.

The protoplasmic growth principles probably also play an important rôle with regard to processes of regeneration in the organism. The protoplasm of an organism may be recognized as a system. A dissolution of continuity develops the accumulation of growth principles in certain cells which causes multiplication until the connection is again established and proliferation ceases.

The malignant tissue cells behave in a quite different manner. These cells are characterized by this fact, namely, that they are not subject to the control of the organism as are the normal tissue cells. The malignant tumor cells may either be capable of utilizing the desmones of all cell types (heterotopic growth) or they are able to build up themselves the principles necessary for their growth independent of other cells. Single tumor cells are capable of multiplying in surroundings, where the same cells, had they been normal, could not have done so.

REVIEWS.

HUMAN PATHOLOGY: A TEXTBOOK. By HOWARD T. KARSNER, M.D., Professor of Pathology, School of Medicine, Western Reserve University, Cleveland, Ohio. Pp. 980; 463 illustrations, 20 in color. Philadelphia: J. B. Lippincott Company, 1926.

THE advent of a new textbook on a major medical subject, written by a recognized authority, is always a matter of importance to medical education and literature, and especially so in pathology where existing textbooks in English perhaps do not cover the field as thoroughly as is done in some other languages. With Dr. Karsner's known interest in "dynamic" pathology, it was to be expected that this phase would receive especial attention, and indeed he announces that his purpose is "to present the morphologic alterations incident to disease, in the light of modern views as to their functional significance."

How far has it been possible to realize this ambitious program within the limits of a single volume of less than a thousand pages? While agreeing with Dr. Flexner in his introduction, that the book provides a well-considered and successful compromise, we recognize certain items in which it falls short of one's desires. Thus rheumatic fever has had to be dismissed in less than half a page, and monsters just as summarily, the pathologic anatomy of all the anemias lumped with that of pernicious anemia, and the diaphragm apparently omitted entirely. Possibly these shortcomings, for which we sympathize with rather than criticize the author, can be overcome in another edition in which he is allowed more latitude. In many places, too, even the author's favorite—pathologic physiology—has had to be so reduced that the usual textbook treatment of morbid anatomy is approximated. On the other hand, the author points out that a textbook is only an introduction to the essentials of a subject, and he certainly has augmented this introduction with an extensive, up-to-date and well-chosen bibliography at the end of each chapter.

Presumably the high cost of printing has led the publishers so to reduce the margins that one experiences an uncomfortable sense of crowding; one might reasonably have asked for a less diagrammatic reproduction of many of the histologic illustrations. One notes "lymphcoytes" (p. 205), "urinaro" (p. 240), "cuxis" (p. 289), "Willins" (p. 444), "fenia" (p. 691), "compliment" and "mul-

itlocular" (p. 692), "rhachitis" (in index only), Fig. 195 is upside down, and a few similar errors, but on the whole the typography is excellent.

It will readily be seen that such details are unimportant or unavoidable with the limitations imposed. The style is clear and concise, and the statement authoritative, especially in those fields in which the author has worked personally, and these are by no means few. All who study this book must agree with the introducer that "the author has made a notable addition to the English literature on pathology." E. K.

RECENT ADVANCES IN PHYSIOLOGY. By C. LOVATT EVANS, University College, London. Second edition. Pp. 366; 70 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $3.50.

WITH the exception of a slight addition to the chapter on Insulin, this edition is practically identical with its predecessor. It presents a brief, concise and fairly up-to-date account of a wide range of topics in physiology. The author devotes almost half the volume to blood and circulation. The remainder considers to some length tissue oxidation, the physiology of muscular contraction, the endocrines and certain reflex mechanisms. The book should be of value particularly as a general resumé of certain work too recent to have been included in the standard texts. E. L.

ATLAS OF THE HISTORY OF MEDICINE: I. ANATOMY. By J. G. DE LINT, Lecturer on the History of Medicine, University of Leiden. Pp. 96; 199 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $6.00.

ANY reasonably intelligent member of our profession would like to know more about its history, if only he had more time or knew where to find the material, or had the price and so on *da capo*. Must we, then, follow the latest developments of the daily press and offer the material in picture form, easily and quickly assimilated and appealing to that childlike love of pictures which persists in most of us through life? If so, this atlas of anatomy should prove more efficient in arousing the historical curiosity of the average medico than more learned or wordy tomes, and, if for no other reason, is worth while. Singer's philosophic introduction also delivers a strong stimulus in its short two pages.

For confirmed followers of *Clio Medica*, this atlas, by the next president of the International Congress on Medical History, is also

desirable. Its two hundred illustrations and legends (biographic, bibliographic and illustrative of anatomic procedure) present for the first time, and in English, a pictorial history of this "basic discipline of all medical science" in convenient and useful form and include not a few illustrations that are difficult for the ordinary student to find elsewhere. The illustrations are well chosen and adequate, though some have suffered in the process of reproduction and are so compactly put together that much craning of the neck is necessitated. The atlas is a worthy supporter of the renewed interest that is being shown in the history of medicine, and it is hoped that the promised volumes of the panorama will soon be forthcoming. E. K.

OPHTHALMIC YEAR BOOK 1926. Edited by WILLIAM H. CRISP, Pp. 315; 9 illustrations. Chicago: Ophthalmic Publishing Company, 1926.

THE 1926 *Ophthalmic Year Book* (vol. 22) comprises thirty-two chapters with nine illustrations. It brings the literature up to date, by reviewing all the domestic and foreign magazines, not alone ophthalmic, but also general.

At the beginning of each chapter there is a bibliography covering the literature therein.

The classification of the abstracts, with each author's name and reference number at the beginning, makes this volume most useful for any one wishing to keep abreast of the literature. H. S.

PRACTICAL DIETETICS IN HEALTH AND DISEASE. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Second revised edition. Philadelphia: F. A. Davis Company, 1926. Price, $4.00.

THIS book is a compendium of dietaries. Detailed lists of foods recommended, as well as those to be avoided, for almost all the ills known to man are set forth in good type. Clearness, simplicity in arrangement of subject matter and a good index commend the book to the busy reader. The rationale of the specific diets, however, receives little or no consideration, and the reader is left quite in the dark, usually, as to why one particular diet is preferable to another. Although its appeal is thus limited, the volume is useful as any encyclopedic presentation of facts may be. T. M.

THE ABDOMEN IN LABOR. By NORMAN PORRITT, M.R.C.S., L.R.C.P. (LOND.), Consulting Surgeon, Huddersfield Royal Infirmary. Pp. 73; 29 illustrations. London and New York: Humphrey Milford; Oxford University Press, American Branch, 1926. Price, $1.75.

THIS rather curious little monograph on a sometimes neglected method of diagnosis in obstetrics represents the author's observations on many parturient women. A rather interesting essay by a general practitioner which won the Sir Charles Hastings Prize of the British Medical Association in 1926. P. W.

THE PATHOLOGY AND TREATMENT OF DIABETES MELLITUS. By GEORGE GRAHAM, M.A., M.D., F.R.C.P., Assistant Physician, St. Bartholomew's Hospital. Second edition. Pp. 230. New York: Oxford University Press, American Branch, 1926. Price, $2.75.

THE second edition of this work embodies some of the important recent investigation in the fields of carbohydrate metabolism and the insulin treatment of diabetes mellitus. The physical, chemical and metabolic properties of insulin are discussed.

More emphasis is given to the importance of urinary sugar than is usual among American diabetitians. Again the alveolar air CO_2 determination, now seldom used in this country, is given a prominent place in the diagnosis, and in following the treatment in diabetic coma, while the CO_2 capacity of the plasma is dismissed with but the mention that "it is not so easily carried out as the estimation of the alveolar CO_2." Author and subject indices together with the bibliography appended to each chapter make the book a very practical starting point for study of the various phases of this subject. W. S.

THE PHYSIOLOGY OF THE CONTINUITY OF LIFE. By D. NOEL PATON, Regius Professor of Physiology, University of Glasgow. Pp. 226; 79 figures. London and New York: Macmillan & Co., Limited, 1926.

THIS book is the outcome of lectures given to classes of medical students. In it are assembled many recent observations and views on the processes going on in the various periods in the life history of the individual. These concern especially the leading factors in reproduction, growth and differentiation. Two interesting chapters are "The Influence of the Gonads upon the Soma" and "The Influence of the Soma upon the Gonads." In his effort to avoid accepting dogmatic statements, the author debates such questions

as spontaneous generation, the Mendelian laws of inheritance, chromosomes as carriers of hereditary characters and the transmission of acquired characters. By this method he hopes to arouse a more critical attitude in the minds of the students toward the unqualified statements in the textbooks. W. A.

THE TREATMENT OF THE ACUTE ABDOMEN, OPERATIVE and POSTOPERATIVE. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.). Pp. 238; 146 illustrations. New York: Oxford University Press, American Branch, 1926, Price, $3.50.

THE author states in his preface that this book is written primarily to help those doctors who are not much practised in abdominal surgery, but who may be called in an emergency to operate upon an acute abdominal condition. The book fulfills this requirement thoroughly, and, in fact, contributes much that can be of great value to men of vast experience in work of this kind. It should appeal also to that great group of young physicians, namely, the hospital intern and resident. So many of the simpler matters of technique are not brought out thoroughly and carefully in our large works that take up the subject in its wider scope. This little book may be considered in the light of a primer and a good one at that. In the vast majority of instances illustrations are well chosen and really show what they are intended to describe. The text presents the author's thoughts clearly and well, at the same time limiting the description to one method of treatment, the one that in the author's hands has given the best results. The book in this respect is unique and exceptionally valuable to the beginner because of its simplicity. The entire work is concerned merely with the treatment of the acute abdomen and does not touch upon the diagnosis. Were the reviewer to offer a criticism, it would be that one chapter be added on the diagnosis of the abdominal emergency.

E. E.

WHY INFECTIONS? By NICHOLAS KOPELOFF, New York State Psychiatric Institute. Pp. 182; no illustrations. New York City: Alfred A. Knopf, 1926.

THE first half of this book defines and describes the usual sites of focal infection. It seems a little too technical to hold the attention of its intended lay reader. The second half deals with the rôle of focal infection in generalized disease, stressing the difficulty of search and the uncertainty of result, once infected tissue is removed. Surgery is advised only when tissue has been repeatedly proved harmfully infected. The chapters dealing with mental disease and practical problems are especially praiseworthy. C. L.

BOOKS RECEIVED.

DeLamar Lectures, 1925–1926, of the School of Hygiene and Public Health, Johns Hopkins University. Pp. 220; illustrated. Baltimore: Williams & Wilkins Company, 1926. Price, $5.00. (To be reviewed later.)

Early Days of the Presbyterian Hospital. By D. BRYSON DELEVAN, M.D. Pp. 192; 34 illustrations. New York: Presbyterian Hospital in the City of New York, 1927. Price, $1.50.

Exophthalmic Goitre. By JOHN EASON, M.D., F.R.C.P.E. Pp. 215; 34 illustrations. Edinburgh: Oliver and Boyd, 1927. Price, 12/6. (To be reviewed later.)

Elements of Surgical Diagnosis. By SIR ALFRED PEARCE GOULD. Sixth edition reviewed by ERIC PEARCE GOULD. Pp. 739; 20 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, $5.00.

Hewats' Examination of the Urine. Revised by G. L. MALCOLM SMITH. Pp. 228. Seventh edition. New York: Paul B. Hoeber, Inc., 1927. Price, $1.50.

South America. By FRANKLIN H. MARTIN, C.M.G., D.S.M., M.D., LL.D. Pp. 435; illustrated. New York and Chicago: Fleming H. Revell Company, 1927. (To be reviewed later.)

Clinical Neurology for Practitioners of Medicine and Medical Students. By EDWARD A. STRECKER, A.M., M.D., and MILTON K. MEYERS, B.S., LL.B., M.D. Pp. 410. Philadelphia: P. Blakiston's Son & Co., 1927. Price, $3.50. (To be reviewed later.)

This Business of Operations. By JAMES RADLEY. Pp. 96. Cincinnati: The Digest Publishing Company, 1927.

Textbook of Biological Chemistry. By JAMES B. SUMNER, PH.D. Pp. 283; 6 illustrations. New York: The Macmillan Company, 1927. Price, $3.50. (To be reviewed later.)

A Primer for Diabetic Patients. By RUSSELL M. WILDER, M.D. Pp. 134. Third edition. Philadelphia: W. B. Saunders Company, 1927. Price, $1.50. (To be reviewed later.)

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Gentian Violet and Acriviolet in the Treatment of Pernicious Anemia.—H. MILTON CONNOR (*Med. J. and Record*, 1927, **125**, 9) reports on the treatment of 18 patients with pernicious anemia by means of gentian violet and acriviolet alone or in combination. In every case, he has had a good result. The gentian violet is given in a solution of 1 to 1000 and 50 or more cubic centimeters of the solution are taken three times daily. The acriviolet has been used in only 4 cases. The dose of this has been 0.1 to 0.4 gr. in enteric capsules. He feels that the occurrence of such marked remissions as his report indicates and that the absence of recurrence in so many cases is more than a coincidence. However, he very conservatively states that his series is too small and the time too short since the inception of treatment to draw positive conclusions. Connor should, in a short time, have a large number of cases to report upon, as the number of patients who come to the Mayo Clinic suffering from pernicious anemia is very large.

Studies in Red Blood Cell Diameter. II. In Pernicious Anemia. Before and during Marked Remission, and in Myelogenous Leukemia.—In the second communication from the Boston group of hematologists, DONALD N. MEDEARIS and GEORGE R. MINOT (*J. Clin. Invest.*, 1927, **3**, 541) make a report upon the diameter of the red blood cells during the remission of pernicious anemia. It has been found that during the spontaneous remission the diameter of the red cells becomes normal, as observed in 11 cases and even less than normal in 3 cases. This is an interesting observation and may help to mitigate the general use of this method of the study of the red cells. The authors also report upon the measurement of the red cells in 9 cases of chronic myelogenous leukemia and 2 cases of subacute aleukemic myelogenous leukemia. In these conditions the red cells were small in diameter, typical of the picture

that is seen in secondary anemia. In 1 of the cases of this type, however, there was a well-marked increase in the size of the cells during the latter part of the disease.

The Mechanism of the Action of the Hydrogen Ion upon the Cardiac Rhythm.—(*J. Clin. Invest.*, 1927, **3**, 555) E. COWLES ANDRUS and EDWARD P. CARTER have previously reported that it is possible to control the rate of the sinus rhythm by changing the pH of the Locke perfusate. In the present study, effects of C_B of the perfusing fluid have been studied, as well as the effect of increasing the carbonic content of the acid of the perfusate. They conclude that the changes in the rhythm of a dog's heart are not due to alteration in the ionization calcium and they show that increased carbonic acid content with perfusate without change in the pH increased the spontaneous development and the propagation of the excitatory process. They conclude from these studies that the difference in the hydrogen ion concentration within and without the cell is the factor controlling this excitation, as the cardiac tissue is particularly sensitive to alterations in the hydrogen ion concentration.

Digitalis and Diuretics in Heart Failure with Regular Rhythm, with Especial Reference to the Importance of Etiologic Classification of Heart Disease.—It has been the view of many cardiologists that digitalis affects very largely congestive heart failure when there is auricular fibrillation, but there is some divergence of opinion as to the value of the drug in heart failure with normal rhythm. Moreover, the etiology of the heart condition has not been considered in the response of the heart to digitalis. MARVIN (*J. Clin. Invest.*, 1927, **3**, 521) has made a careful clinical study of the effects of digitalis alone and also in conjunction with diuretics. He shows in the results of his studies that digitalis in large doses in patients with advanced congestive heart failure and regular rhythm brings about consistent improvement in the group of heart cases which are designated as arteriosclerotic heart disease. It has some effect on the patient with syphilitic heart disease, but practically no effect in rheumatic heart disease. The same statement applies to the relief of edema by means of diuretic drugs after complete digitalization. Effective diuresis is accomplished in arteriosclerotic heart disease, whereas in rheumatic heart disease such is not the case. The author suggests that the difference of opinion that exists concerning digitalis in heart failure with normal rhythm may be the result of variations of the etiology of heart failure in the patients selected for treatment. He believes that if an etiologic diagnosis was made in each case, it would be possible to attain proper correlation of the results attained by various observers.

Auscultatory Percussion in the Diagnosis of Pleural Effusion.—Physical signs of disease of the thorax are for the most part standardized, and it is only occasionally that some observer of unusual clinical acumen develops or discovers some new sign which may be of value in the diagnosis of intrathoracic conditions. WEBB (*J. Am. Med. Assn.*, 1926, **88**, 99) describes a method of auscultatory percussion in the diagnosis of pleural effusion, which promises to be of great value,

more particularly the differentiation of this disorder from a thickened pleura or advanced tuberculous lesions at the base of the lung. The method, in brief, is to note, when an effusion is present, a higher and shorter pitched note upon percussion of the spinous processes of the vertebræ with the bell of the stethoscope in the axilla.

SURGERY

UNDER THE CHARGE OF

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New Research in the Etiology of Cancer, with Reference to the Work of Gye.—SITTENFIELD (*Am. J. Roentgenol.*, 1926, **16**, 525) asserts that the germ theory of cancer is not a new one. Often has it been advanced and as often been rejected. It has been pointed out that it does not explain cancer. This view was justified because no one had isolated an organism, which when injected into an animal would reproduce with certainty a new growth. Opponents of the germ theory are correct, if their contention rests purely upon the basis that the cancer question cannot be solved by setting up wholly an extrinsic bacterial origin. In this much Gye agrees that the extrinsic agent or virus by itself is incapable of producing malignant tumor formation. To do that it requires the coördination of the intrinsic factor or accessory substances produced by the cells themselves. The intrinsic factor or accessory substance varies from tissue to tissue and also from tumor to tumor. The outstanding feature of this new research is the supposition of the close association of this accessory factor with an infective agent. The physical and chemical properties of the so-called accessory factor are as yet not established, but possibly more knowledge of both agents may yield vital facts in the etiology of cancer, as, for instance, sex or age incidence, selective localization, the effect of chronic irritation and the relationship between benign and malignant tumors.

Undescended Testicle.—MEYER (*Surg., Gynec. and Obst.*, 1927, **44**, 53) reports that the exact etiology of undescended and ectopic testicle has not yet been definitely settled. The histologic changes point to the fact that the spermatogenic cells are present and functionate in about 10 per cent of all cases. The interstitial cells which have to do with the development of secondary sexual characteristics are always abundantly present. Since these findings are almost constant, the undescended testicles should always be saved. Secondary complications occur. Malignant degeneration is not as frequent as is generally

supposed and fear of the same is no indication for orchidectomy. Chronic inflammation, the presence of a potential or real concomitant hernia, practically always present, torsion of the spermatic cord and strangulation of the testicle are occurrences so frequent that surgical interference is always indicated. The best time to operate is before puberty, between eight and ten years of age. Torek's method of orchipexy is the best means of curing the hernia and placing the testicle into its normal position. It is logical and surgical, maintaining full blood supply to the testicle which comes to lie in the bottom of a well-formed scrotal sac.

Gastroduodenostomy.—FLINT (*Lancet*, 1927, i, 12) says that he has practised this operation for chronic duodenal ulcer in a series of close to 200 cases. He emphasizes that it is quite easy to mobilize the duodenum in practically every case. He has performed gastroenterostomy only nine times, largely on account of adhesive difficulties. In all the other cases mobilization was easily accomplished. One detail in technique is important, that is, to free the angle between the second and third parts of the duodenum, where it turns to the left to cross the spine. It is better to free this end of the second part, rather than the upper angle, where the first and second parts meet, as at this point there is often very embarrassing vessels. There have been 2 deaths in this large series. There have been no instances of attacks of discomfort, flatulence and diarrhea following indiscretions in diet. No anastomatic ulcers have occurred in the author's experience when doing gastroduodenostomy for chronic duodenal ulcer. The more physiologic disposition of the parts after gastroduodenostomy probably accounts for the complete freedom from trouble after operation.

The Importance of Toxemia Due to Anaërobic Organisms in Intestinal Obstruction and Peritonitis.—WILLIAMS (*Brit. J. Surg.*, 1926, **14**, 295) writes that the hypothesis put forward in the paper is that the toxemia in cases of intestinal obstruction, whether organic or secondary to peritonitis, results in part at least from the absorption of the toxin of Bacillus welchii, due to the proliferation of this anaërobe in the stagnant contents of the small intestines. The author discusses the clinical resemblance of the toxemia of intestinal obstruction and peritonitis to that of gas gangrene. Evidence is given of the proliferation of Bacillus welchii in the small intestine in cases of intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. Evidence is given of the presence of Bacillus welchii toxin in the small intestine in intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. The toxin was not found in normal small intestine contents or in contents of the large intestine, even when obstructed in human subjects. Evidence is given compatible with the absorption of Bacillus welchii toxin from the clinical aspect of cases, from the occurrence of hemolysis and from microscopic changes in the heart and liver of fatal cases. The author, moreover, reports a series of cases of appendicular peritonitis and acute intestinal obstruction, in which Bacillus welchii antitoxin was administered. Evidence is given in the results of this therapeutic test of clinical benefit in individual series and of improvement of the general mortality note in each series.

PEDIATRICS

UNDER THE CHARGE OF

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Growth in Children with Diabetes Mellitus.—LADD and DAY (*Am. J. Dis. Child.*, 1926, **32**, 812) studied 34 cases of diabetes mellitus, all but 4 of whom were either overweight or overgrown, or both, at the time of the onset of the disease. No other significant etiologic factor was noted. In the 2 of these remaining cases diabetes appeared after an acute infection; in 1 the disease was apparently idiopathic. Disease observers noted that growth in height in children with diabetes mellitus diminishes or stops completely, depending upon the severity of the case, and this phenomenon appears to be due to lack of food. The stimuli for growth in height seems to persist longer under the adverse conditions of diabetes, and it also appears to be slower in starting than the stimuli for changes in weight. Insulin enables patients to use sufficient food and growth follows. The best weight for the child is the average weight for height, as expressed in the Bardeen growth curve for normal children, allowing for normal variation of ±12 per cent. The best food intake is somewhat less, possibly about two-thirds of the total calories of the Holt and Fales standards. The average proportion of carbohydrates, protein and fat of the total calories is: Carbohydrate, 35 per cent; protein, 15 per cent; fat, 50 per cent. The fat in carbohydrate quotients are just about the reverse of the Holt and Fales standard. This is not necessarily the best proportion. Through experience during the last few years, the authors believe that in some cases proportions nearer the normal as given by Holt and and Fales yield excellent results. They also feel that regularity in food intake and insulin dosage, both as to amount and to time of ingestion is absolutely essential to the successful progress of the patient.

A Comparison of the Effects of Supplementary Feedings of Fruit and Milk on the Growth in Children.—MORGAN, HATFIELD and TANNER (*Am. J. Dis. Child.*, 1926, **32**, 839) examined 47 children living in the California state schools for the deaf and blind during a period of eighteen weeks in the spring of 1925. During this period 13 of these children were given a half pint of milk each day as a supplementary lunch, 13 were given one medium large orange each day, 10 were given four pulled figs each and 11 were used as controls. The degree of underweight, lack of fitness, of these groups when the feeding was begun was in decreasing order—orange, fig, milk and control. Five of the fig group, 2 of the orange group, 1 of the milk and none of the control group suffered an attack of influenza during the experiment. All of the children were served with the same regular meals throughout in the institution's dining room. Judged by the Baldwin-Wood standard

of nutrition, after fourteen weeks of supplementary feeding the milk, orange and fig groups had made almost exactly the same amount of improvement, while the control group had increased only a quarter as much as the other three. Judged by the Pirquet standard, the orange group made the most improvement, the fig and control group about half as much and the milk group had fallen off a little. Judged by the Dreyer standard, the orange group again made the most growth, the control and milk each about half as much and the fig least of all. The average of all these gains shows the orange group first, the fig and milk next and the control group last. The gross gain in pounds was largest for the milk group and the average percentage gain in weight above that expected, according to the whole standard, was largest for the orange and milk groups. Seven children were changed from the milk to the orange lunch, and 7 from the orange to the milk lunch at the end of fourteen weeks, and these feedings were continued for four weeks longer. All gain in weight was considerably decreased in those changed from orange to milk, but very little affected in those changed from milk to orange. The percentage of the original groups showing an increase after fourteen weeks, in standing and sitting, height was greatest in the milk group; in chest circumference, chest expansion and vital capacity, in the fig group; in hand-grip strength, in the orange group. The composition of the house diet was shown to be excellent as to milk and animal protein content, fair as to vegetable content, but somewhat deficient in fruits, especially of the fresh, raw variety. The ash reaction of the diet as eaten was, undoubtedly, acid, and it is possible the supplementing of this as well as of the antiscorbutic content of the diet with the oranges were effective. The value of the figs may lie in their laxative action. The value of extra milk for these children must lie chiefly in the extra caloric value as well as the supplenting of a possibly uneven intake of milk at meals.

Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1926, **32**, 862) reports the result of the study of 100 consecutive cases of asthma, in which he found that 22 per cent of the patients had eczema, 7 per cent had urticaria and 2 per cent had angioneurotic edema, making a total incidence of 21 per cent. Urticaria and angioneurotic edema secondary to an eczema were not included in these figures. In 7 to 9 of these patients who were protein sensitive the incidence of eczema was 22 per cent; urticaria, 2.5 per cent; angioneurotic edema, 2.5 per cent. In 21 who were protein nonsensitive the incidence of eczema was 19 per cent; urticaria, 24 per cent; there were no cases of angioneurotic edema. The patients composing the group of allergic asthma type accounted for 55.8 per cent of the total food sensitization. Of these, 7.5 per cent gave no food reaction, another 7.5 per cent reacted only to one or two foods, while the remaining 12 per cent accounted for 52 per cent of the total food reactions. The last group always reacted to foods in biologic groups and the dermatoses were always either eczema or angioneurotic edema. The patients with urticaria did not react to biologic food groups. Eczema always commenced during infancy and always proceeded the onset of asthma varying from one to seven years. Angioneurotic edema was concurrent with or followed the onset of asthma. Urticaria always occurred after the onset of asthma. This relation

did not exist in the non-allergic group. Patients with asthma, showing a positive cutaneous food reaction whose eczema had cleared, did not have the recurrence of the asthma with the ingestion of these sensitizing foods. Ingestion of these foods did cause urticaria or angioneurotic edema and occasionally asthma in some cases. Patients with persistent or recurrent eczema were not relieved of the skin condition by elimination of these foods from the diet, but other ingestion resulted in exacerbation of the eczema, and especially in those who were sensitive to biologic food groups. The foods responsible for the greatest number of skin reactions in the dermatosis group were fish, meat, milk and egg. All children with asthma reacting to fish or meat as biologic groups invariably give a history of eczema commencing during infancy. The existing clinical manifestations of hypersensitiveness to fish were mainly referable to the skin and were urticaria, erythema and angioneurotic edema. Hypersensitiveness to meat was manifested in the respiratory tracts; to egg in the gastric intestinal and respiratory tracts and to milk in the gastric intestinal tract and the skin. In infants and young children with eczema reacting to food as a biologic group, it may be possible to prevent asthma by further tests and by elimination of an allergic sensitization which have a direct bearing on the etiology of asthma.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Decline in the Registered Mortality from Syphilis in England—To What is it Due?—This is a notable summary by a public health authority, NEWSHOLME (*J. Social Hyg.*, 1926, **12**, 513), of international reputation in the field of venereal disease control, on the progress made in the control of syphilis, as evidenced by the British mortality figures from 1901 to 1925 and the registration in British venereal disease clinics from 1918 to 1925. It appears that the crude annual death rates from syphilitic infections at all ages per 1,000,000 living, as given in Table L of the Registrar General's annual review of England and Wales for the year 1924, indicates that the mortality from syphilis has fallen from 53 in 1901 to 33 in 1924. Mortality from general paralysis of the insane has fallen from 70 in 1901 to 40 in 1924; that from tabes dorsalis has slightly increased from 13 in 1901 to 19 in 1924; aneurysm has decreased from 30 to 26; the combined rate from 166 to 118, and relative figures from 100 to 71, in this lapse of time.

The most striking change is apparent beginning with 1919, when all the rates exhibited the most pronounced drop apparent in years, a decline which has been held consistently or become more pronounced between 1919 and 1924. Sir Arthur Newsholme points out that a revision of these figures, such as Osler suggested, to include the occult death factor from syphilis, would place the disease, with cancer, tuberculosis and pneumonia, as one of the four chief causes of death. The drop in mortality figures has taken place in the face of improved diagnosis and more complete registration. The decline in death rate of 1924 as compared with 1921 amounts to 29 per cent, and when 1917 is compared with 1924 it amounts to 32 per cent. Sir Arthur indicates that the changes in mortality from late complications are indices of the effectiveness of treatment begun a decade ago, while the more recent changes in registered mortality from syphilis as such indicates the effectiveness of the World War campaign. An equally interesting evidence of the effectiveness of the British antivenereal campaign is found in the decline of new cases of gonorrhea and new cases of syphilis in the face of an increased number of clinics and a steadily increased total attendance from 1918 to 1925. In 1917 the total number of government clinics was 113, increased to 193 in 1925. The total attendance increased from 204,692 to 1,719,148. New cases of syphilis in 1918 were 26,912; in 1919, 42,134; in 1925, 22,588. Gonorrhea, on the other hand, has shown a smaller decline, probably because of the lesser effectiveness of medical treatment control in this disease. An interesting incidental observation concerns the comparison of the experience of Portsmouth and Birmingham. In both of these cities there has been a fairly parallel and equal diminution of cases of syphilis and gonorrhea, yet in one of them disinfection as a prophylactic has been publicly advocated and in the other it has not. The author compares his findings with those of Bayet, of Brussels (*La Lutte contre le syphilis en Belgique*, 1926), in which essentially the same experience is recorded for Belgium. The chief feature of the work accomplished in both countries has been *prophylaxis by treatment*. Bayet concludes that arsenical medication has reduced the contagious period in syphilis from three-quarters to four-fifths, although the author questions the accuracy of this estimate. As they stand, the figures constitute the greatest encouragement to workers for veneral disease control which has thus far appeared.

Observations upon the Regulation of Blood-flow Through the Capillaries of the Human Skin.—Lewis (*Heart*, 1926, **13**, 1) investigated the statement of Ebbecke, that when the hand of a susceptible subject is watched in strong sunlight or otherwise warmed whitish and red spots of a few millimeters in diameter are often to be seen. He studied these patterns with a view to determining their permanency. Krogh states that they may continually change in location; Mackenzie, speaking of larger mottlings on the arms and legs, states that they may vary within a few minutes from pallor to congestion. These statements create the impression that the capillaries of the skin are in a constant state of movement individually and in groups, the mottling of the skin changing unceasingly. Comparisons are drawn with the state of capillary activity of the circulation, as described by Krogh on the frog's

web and by Richards on the glomeruli of the kidney. After careful mapping of the pallor patterns and microscopic observation of the behavior of the vascular supply, the author is unable to support the belief that mottling of the skin (livedo) is materially changed by external temperature or heavy venous congestion. Moreover he found little evidence of internal or spontaneous variation from hour to hour or day to day, provided the skin remains under reasonably constant conditions. The tone of the minute vessels, terminal arterioles, capillaries and minute venules treated as a whole is influenced locally by the needs of the tissues which they supply. Friction may cause temporary alteration in the pattern. There is insufficient evidence that any endothelial vessel of this meshwork is influenced as an individual by local needs to an extent which affects very appreciably the flow of blood through it. Owing to the freedom of diffusion in the tissue spaces the influence of local nutrition is exerted over a wider range than this, the vessels being affected as groups rather than individually. There appears to be peripherally a balancing mechanism between the meshwork of minute vessels and the muscular arterioles, whereby a change in the caliber of vessels of the second order, which more than meets the requirements of the tissue supplied, is met by a contrary change in the vessels of the first order. The bloodflow to the tissues is regulated in a twofold manner—by the tone of arteries and muscular arterioles on the one hand; by the tone of endothelial vessels on the other. The first mechanism is under the governance of the nervous system, central and peripheral, and forms a coarse adjustment; the second is controlled more directly by the local tissue needs and forms a fine adjustment of great precision. Mottling of the skin of the palms of the hands and of the skin of the body generally (cutis marmorata) is due to local differences in the tone of the minute vessels. These differences are to be coupled with the subdivision of the skin into anatomical areas, the latter being possibly areas of the skin to which the distribution of blood through arterioles is unequal.

OBSTETRICS

UNDER THE CHARGE OF

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When Shall We Treat Retroflexio Version of the Uterus and How?—ANSPACH (*Atlantic Med. J.*, 1927, **30**, 214) deals concisely with the

subject and brings up to date the opinions gathered from the mass of literature dealing with these abnormalities. The symptomatology and methods of correction are given in detail. The author gives his attitude regarding retroflexio version in that this condition should be let alone in cases of unmarried women where there are no complications and no symptoms. Further, that it should not be allowed to continue in the married woman who is desirous of children. He states there is nothing which is more often responsible for abortion in young married women than this abnormal condition existing in the uterus. The symptoms of retroflexio version need particular and careful study, so that one may be able to differentiate between retroflexio version and other lesions. The most frequent symptoms given in their order of frequency are backache, lower abdominal distress, menorrhagia, dysmenorrhea, vesicle and rectal disturbances. The first two given are by far the most frequent, and the author lays stress on other conditions which are associated and factors in combination with the abnormality itself. The backache and lower abdominal distress which are particularly due to retroflexio version are definitely aggravated by exertion and relieved by rest. The article goes into the correction of the lesion, the use of the pessary which is often unappreciated, much maligned, misunderstood and badly managed. The operations are not taken up in detail but the principle which underlies many of the operations for this correction are mentioned, and the principles involved for the satisfactory correction are set forth.

Forceps Delivery.—CORNELL (*Surg., Gynec. and Obst.*, 1927, **44**, 221) sets forth certain conditions which should be observed before instrumentation and forceps delivery are considered. They are given in their order and explained in the text: (1) The cervix should be fully dilated or dilatable, if not disastrous results will follow; (2) the membranes must be completely ruptured; (3) the child should be alive, although there is an exception to this rule—the extraction of a dead fetus by forceps is sometimes permissible; (4) the head should be engaged and never floating; (5) the mother's condition should be such that a general anesthetic is not contraindicated; (6) the pelvis should be large enough to permit passage of the child. Stress is laid on the prolongation of the second stage of labor which may result in cerebral injury to the child and maternal exhaustion. The technique of preparation is given in detail. For an anesthetic chloroform is ruled out; the author mentions ethylene as a general anesthetic, and is of the belief that ethylene causes the tissues to bleed more readily. Careful instructions are given for catheterization. A comprehensive description of the ironing out or stretching of the perineum is set forth. Rectal examinations are not used. Mid forceps and low forceps are described; high-forceps operations are not performed because of the greatly increased fetal mortality and the severe maternal lacerations and trauma which follow its use; he wisely prefers a version and extraction of these cases, as giving better results. The author describes the episiotomy when performed and the manual rotation of the posterior positions. The completion of the labor after delivery of the head is given in detail and the immediate medication and after treatment, along with the repair of of the episiotomy.

Bradytocia.—A term seldom used in obstetrics, and deals particularly with and applies to those long, drawn-out and tedious cases of labor, is bradytocia. It differs from dystocia in that it is not pathologic labor. Five hundred cases of bradytocia were selected by HORNER (*Surg., Gynec. and Obst.*, 1927, **44**, 194). The incidence of bradytocia was 10 per cent on over 4000 deliveries, of the time limits which were set as twenty hours for primiparæ and fourteen hours for multiparæ. One case in every 10 was prolonged labor. The highest percentage was found among American born, being 60 per cent. It occurs more frequently in primiparæ, between the age of nineteen to thirty years. No definite etiologic factor is given, but a combination of conditions that influence the prolongation of labor are given for its existence. Chief among them are the early rupture of membranes, over term pregnancies and primary inertia. A deficiency of innervation of the uterine musculature in the young gravidæ seems to delay the function of the uterus when labor begins. The diagnosis of bradytocia begins in the prenatal period by the general examination of the patient's physical construction, pelvic anatomy and in the latter months by fetometry. The maternal morbidity in prolonged labor is necessarily high, as a prolonged labor lowers the patient's resistive power and consequently reduces her chance of withstanding infection. Watchful expectancy of these cases is at present the method of choice, but the future may hold some change as time and methods advance. The conclusions drawn are those of prophylaxis. The selecting of cases unfit for normal labor. The test of labor and its essentials as to what is a sufficient test of labor. The operative interference and justification in its procedure. The shortening of the first stage of labor if possible and the termination of the second stage after a lapse of two hours. There is still much to be discussed and adjusted in handling bradytocia cases.

GYNECOLOGY

UNDER THE CHARGE OF

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Roentgenography of the Fallopian Tubes.—In presenting their technique and experiences with the injection of lipiodol for the purpose of making roentgenograms of the Fallopian tubes, MCCREADY and RYAN (*Am. J. Roentgenol.*, 1926, **16**, 321) state that the unsatisfactory results of operation for the relief of sterility depend largely upon the inability of the gynecologist to make an exact diagnosis of the actual pathologic condition of the tubes before operation. It necessarily follows that many cases are operated upon uselessly. Until the advent of the

Rubin test, even the diagnosis of patency of the tubes was not possible. Insufflation of the tubes was a marked advance, but even this test does not indicate the point of occlusion, a very important factor in determining the indication for operation. The farther out from the uterus the occlusion exists, the better the chances for the success of the operation. They believe that the results of roentgenography of the tubes can be thoroughly relied upon if conducted with proper care and attention. This method will not only make the diagnosis of patency, but if the tubes are obstructed the point of occlusion can be accurately demonstrated. They describe their technique, which is quite simple, and presents many beautiful examples of visualization of the tubes, both normal and pathologic.

Hemorrhage of Puberty.—The menstrual irregularities and hemorrhages which occur at the time of puberty have always been of much interest to the gynecologist, and until quite recently have often been rather troublesome to treat successfully. It is of interest, therefore, to review a study on this subject which was made by WOLFE (*Am. J. Obst. and Gynec.*, 1926, **12**, 45), as the result of which he states that puberty hemorrhage is a definite clinical entity presenting as a menorrhagia or metrorrhagia in the absence of inflammation, neoplasia or the pregnant state. The soft patulous cervix is pathognomonic; the body may or may not be enlarged. Symptoms recur after curettage, but are always controlled by radium. Curettings are abundant, thickened and frequently polypoid. This is the result of a diffuse glandular, stromal and vascular hyperplasia. Persistence of solitary ripening follicles or simultaneous maturation of multiple follicles accentuates a physiologic endometrial hyperplasia into a pathologic type. These changes have been experimentally reproduced in laboratory animals. Corpus luteum formation is absent. The uterus is the direct seat of bleeding. It results from thrombosis of the endometrial vessels and ensuing necrobiosis, and from actual mechanical rupture of engorged capillaries. The factors inaugurating persisting, follicular cysts in the ovary with its concomitant endometrial hyperplasia remain a subject for future study.

Results of Operations for Uterine Prolapse.—One of the most important contributions that the large clinics can make to the progress of surgery is the periodical analysis and report on the end results which are obtained following various operative procedures. In the days before follow-up clinics were held, many patients were discharged from hospitals as cured, but in a short time the original trouble returned and the surgeons were never aware of their failures and consequently had distorted ideas of the value of certain operations. A comparative study of the end results of the various operations for prolapse of the uterus done between 1915 and 1925 at the Woman's Hospital in New York has been presented by BULLARD (*Am. J. Obst. and Gynec.*, 1926, **11**, 623) in which there are 361 cases which were operated upon by 30 different operators. Every patient had been examined by the surgeon who operated upon her and by some other member of the visiting staff at least once since her operation and a large majority of them have been observed several years in the follow-up clinic. The survey shows that

95 per cent of the cases are cured by vaginal plastic surgery. The vaginal plastic work combined with ligament shortenings from above is satisfactory perhaps in cases of slight prolapse, but the careful fascial reconstruction by vagina undoubtedly is responsible for the success. He states that the majority of the gynecologists of today have long since ceased to attempt to cure descent of the uterus by any form of suspension or fixation by the abdominal route. Careful reconstruction of the various planes of the pelvic fascia that have become attenuated, overstretched or torn is the *sine qua non* of the operative treatment of prolapse. In this series the Watkins operation has not been followed by enterocele but there is a considerable percentage of cases with bladder symptoms. The Mayo operation has been extremely satisfactory except for an occasional enterocele. Vaginal hysterectomy has been most satisfactory.

Cervical Cauterization Preceding Hysterectomy.—The theoretical danger of the retained cervical stump following hysterectomy has been handled by CASHMAN (*Am. J. Obst. and Gynec.*, 1926, **12**, 591) for some years by the use of the cautery. He uses it not only as a preliminary to hysterectomy but also in practically all operations for infected tubes and in cervicitis without intraäbdominal complications. He has not seen a case of carcinoma develop in a cervix treated in this manner although he has seen 3 cases in the past two years in patients who had had pelvic operations but in whom a diseased cervix was neglected. The technique which he uses differs from that originally advocated by Hunner since the cauterization is completed at one sitting. The cervix is dilated and the entire cervical canal is cauterized, and deep radial incisions are made at the external os, extending well onto the vaginal portions of the cervix, thus destroying the cone-shaped, gland-bearing portion of the cervix by a simple rapid method. If this be done as the first step is subtotal hysterectomy, there is accomplished practically all that is accomplished in total hysterectomy and the disadvantages of total hysterectomy are eliminated. As a result of this procedure, the cervical mucosa and glands are destroyed, the cervix heals smoothly without a lumen and no after-treatment is necessary and moreover the normal vault of the vagina is preserved.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Optic Nystagmus and its Value in the Localization of Cerebral Lesions.—FOX and HOLMES (*Brain*, 1926, **49**, 333) employ the term "optic nystagmus" to designate that regular movement of the eye

induced by observing figures on a rotating drum consisting of a slow component in the direction of rotation of the drum and a quick component in the opposite direction. Bárány believes the phenomenon is of cerebral origin, and suggested that the slow phase is activated from the gyrus angularis and the quick phase is activated from the frontal lobe. Stenvers believes that it is a cerebral reflex subserved by a path between the occipital pole or the calcarine region and the frontal lobe, and that it is lost toward the opposite side when a lesion damages either of these centers or the pathway between them. The aim of the authors' investigation was to determine if an absence or a modification of optic nystagmus to the one side has any value in the localization of cerebral lesions. Their observations were made on 41 cases of cerebral tumor, in 24 of which the site of the lesion was verified by either operation or postmortem examination. They concluded: "That a unilateral lesion of the forebrain can disturb lateral optic nystagmus to the opposite side only. If the lesion lies in the right hemisphere clockwise rotation of the drum evokes a nystagmus, consisting of slow deviation of the eyes to the left and quick jerks to the right; in other words, a nystagmus to the right; but anticlockwise rotation has no effect, or produces a less regular or less pronounced nystagmus to the left." While to any definite conclusion some of their cases presented obvious exceptions, it seemed that nystagmus to the opposite side is effected when a lesion lies in the supramarginal or angular gyrus, in the adjacent portion of the parietal and temporal lobes, in the posterior end of the second convolution or along the line joining this with the angular gyrus. Their observations tend to support Stenvers' hypothesis, that reflex centers for optic nystagmus lie in the occipital lobe and in the second frontal convolution and that these are connected by a reflex path which runs through the white matter of the hemisphere.

Sclerosis of the Central Artery of the Retina.—Bridgett (*Am. J. Ophth.*, 1926, **9**, 725) made histologic examination of the central arteries of the retina, obtained postmortem, from 200 patients. This examination disclosed normal vessels in 45.5 per cent excessive physiologic thickening in 21.5 per cent, arteriosclerosis proper in 26 per cent, syphilitic arteritis in 1.5 per cent and periarteritis in 5 per cent. The development of the subendothelial layer of the central artery normally reached a maximum about the fourth or fifth decade; excessive thickening, not accompanied by degenerative changes was found in about one-fifth of the arteries. The true arteriosclerotic lesions were similar to those occurring in other vessels of like caliber, but usually a slight degree. The periarterial lesions were most frequently found in relation to local or general infection. Sclerosis of the central arteries occurred only one-third as frequently as did the sclerosis of the aorta, the coronaries and the brain arteries. Conversely, when the aorta, coronaries and brain arteries were grossly normal sclerosis of the central arteries was found in 18 per cent of the cases. In 22 cases histopathologic differences were found between the right and left central arteries. Sclerotic changes occurred a little over twice as frequently in the extraneural as in the intraneural part of the vessels. Considerable disagreement was found to exist between clinical and histologic observations. The fact that vascular sclerosis usually does not involve

the arterial system uniformly deserves emphasis. In retinal arteriosclerosis of persons between the ages of nineteen and forty-two years of age syphilis was the most frequent constitutional disease. In all age groups the number of cases with normal predominated over those with sclerosed central arteries. The incidence of sclerosis was somewhat higher in females than in males.

RADIOLOGY

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Ulcer of the Duodenum.—In considering the problems connected with ulcer, JUDD (*Minnesota Med.*, 1926, **14**, 320) states it is first necessary to separate the gastric from the duodenal. The gastric ulcer may be malignant; in the case of duodenal ulcer the question of malignancy may be disregarded. Primary carcinoma of the duodenum that resembles an ulcer is almost unknown. Ulcers of the duodenum are usually situated on the anterior surface in the cap; occasionally they are found on the lower border and rarely on the posterior wall, some distance from the pylorus. Because of their proximity to the pancreaticoduodenal vessels, ulcers in this region are frequently the cause of severe gastrointestinal hemorrhages. It is not unusual in opening the duodenum to find a small spot of puckering, congested, mucous membrane just opposite the anterior ulcer. Lesions in the duodenum, as seen in the operating room, are of two distinct types—one a true chronic ulcer with a crater, which has lost a certain amount of mucous membrane and the other not a true ulcer but a localized area of inflammation. Duodenal ulcers occur much more frequently in males than in females and patients most often present themselves for treatment at middle age. Jewish people apparently have a greater tendency to duodenal ulcer than do other races. Physiologic activity has to do with the cause of an ulcer and infection with certain strains of bacteria plays an important role. Experimental evidence is that acid secretion comes from the glands at the cardia and that secondary ulcers may follow resection, just as they follow gastroenterostomy. If excision of the ulcer with reduction of the sphincter activity can be performed just as safely as gastroenterostomy, this is the operation of choice. This is dependent on the mobility of the duodenum; if the upper edge of the duodenum is bound down as a result of inflammatory adhesions it is usually not advisable to attempt to excise the ulcer. At present he is excising 50 per cent of duodenal ulcers and has had more than 90 per cent of cases showing complete and permanent relief

from all symptoms. A number of bleeding ulcers continue to bleed at intervals after gastroenterostomy; therefore, the radical operation is preferable in cases of duodenal ulcer in which severe bleeding has occurred.

Massive Collapse of the Lung.—Massive collapse of the lung is a shrunken, airless condition of a part or all of one or both lungs, occurring suddenly after operation or injury below the neck, without the direct application of external force, or demonstrable obstruction of the air passages. Essentially it is the same as pulmonary atelectasis; it differs only in that its onset is abrupt, that it usually is lobar in distribution and that it is intimately associated with some form of trauma. RIGLER (*Minnesota Med.*, 1926, **6**, 326) reviews the literature, crediting Pasteur with first calling attention to the condition of 1890 in cases of postdiphtheritic paralysis of the diaphragm, and in 1908 noting it following abdominal operations. The most reasonable theory would support a combination of respiratory immobility and bronchial obstruction as the cause. The close resemblance of massive collapse and atelectasis following foreign body strengthens this view. Bronchoscopy, with removal of a plug and subsequent cleaning of the collapsed lung, has been done. The onset may be sudden, usually within twenty-four to seventy-two hours after operation or trauma; or, more often, slow with dyspnea and cyanosis the most prominent findings. In the fulminating cases it closely resembles pulmonary embolism. The clinical course is most frequently mild, lasting three to six days. It is notable that no case of unilateral collapse without complications has ever proved fatal. The lung is heavy, shrunken and does not crepitate, the alveoli are collapsed and there may be fluid in the bronchi. The ingress of air is interfered with; the circulation remains intact, the air is absorbed and the lung gradually shrinks down. The diaphragm in the affected side moves upward, the mediastinum moves toward the affected side. The roentgenographic is the best diagnostic method of demonstrating the lesion.

The Newer Clinical Aspects of Gastric Carcinoma.—The traditional conception of gastric carcinoma from the standpoint of diagnosis and prognosis is in need of revision in the light of modern medical progress, asserts EUSTERMAN (*Radiology*, 1926, **6**, 409). The pathologist's conception of the evidence of the malignant transformation of a benign ulcer, and the roentgenologist's recognition and localization of circumscribed lesions, with an estimate of their probable size and extent have made possible earlier recognition of the actual and potential malignant processes in the stomach. Comparing two sets of statistics, one compiled in 1914 by Friedenwald and another from the material of the Mayo Clinic seven years later, he points out that malignant lesions were detected at an earlier and more operable stage in the second series. Exclusive of the more obstructing small lesions, and of some of larger extent in a high-lying stomach, the majority of cases of gastric carcinoma are readily diagnosable as such on the basis of history, physical examination and gastric analysis. Malignant transformation of a benign ulcer may be suggested by: (1) Loss of periodicity of attacks (attacks are longer and intervals of relief shorter); (2) loss of periodicity

of pain, the pain tending to persist after eating; (3) less severe pain, but a more constant dull ache, increased by eating; (4) loss of appetite, which may ensue even when the test meal shows the high acidity characteristic of ulcer; (5) variation in the vomiting, which may diminish in amount and frequency, although it is rarely increased, unless there is obstruction; (6) diminution in gastric acidity; (7) persistent occult blood in the feces. Roentgenologic indications of malignancy, such as the niche type of ulcer with an unusually large crater and the demonstration of ulcerating carcinoma with a meniscus-like crater, constitute a significant advance.

NEUROLOGY AND PSYCHIATRY

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A Case of Herpes Zoster, Apparently Due to Invasion of the Ganglia by Round-cell Sarcoma.—MORTON (*J. Neurol. and Psychopath.*, 1926, **6**, 296) reports a case in which sarcoma cells form nodules on the left side, and had spread and invaded the fifth and sixth dorsal ganglia on the right side (probably through the lymphatics). A disturbance of a herpes zoster due to specific virus formed; it would seem, therefore, that herpes zoster results from injury to the dorsal ganglion whether caused by an acute specific virus or some other form of trauma.

The Operative Treatment of Gastric Crises.—CRITCHLEY and WOLFSOHN (*J. Neurol. and Psychopath.*, 1926, **5**, 318) believe that following a careful review of the cases treated by operative procedures and the study of several cases it is probably necessary to carefully differentiate between crises of vagal and those of sympathetic origin or both. Section of the gastric branches of the vagus combined with gastrojejunostomy possibly affords greatest relief in vagal cases. In sympathetic cases chordotomy, or section of the anterolateral tracts, for relief of pain is least dangerous. In some crises section of the vagus will effect a cure.

Yellow Spinal Fluid Associated with Tumor of the Brain.—COMFORT (*Arch. Neurol. and Psychiat.*, 1926, **15**, 751) states that xanthochromic fluid probably has definite significance in the localization and prognosis of brain tumors, occurring as it did in about 20 per cent of the cases studied. Xanthochromia, probably hemolytic in origin, when associated with tumor of the brain indicates the involvement of the ventricular or external surface of the brain, and that the tumor is soft and vascular or surrounded by engorged vessels. The hemorrhages causing the

coloration are believed to be small and repeated. Xanthochromia occurring with many erythrocytes, indicating a soft vascular tumor, is possibly a contraindication for procedures lowering intraventricular pressure.

Tryparsamid in the Treatment of Late Neurosyphilis.—MOORE and SUTTON (*J. Nerv. and Ment. Dis.*, 1926, **63**, 569) believe that in late neurosyphilis the treatment should be primarily to build up resistance, hence the value of tryparsamid which is too weak a tryponemacide for use in early syphilis. Patients who have received intensive treatment with mercury and arsphenamins show more striking improvement than individuals who have received no preparatory treatment. It should never be forgotten, however, that tryparsamid carries a menace to the optic nerve and suitable tests and examinations should be regularly carried out.

Somnolence: Its Occurrence and Significance in Cerebral Neoplasms.—The value of somnolence as a diagnostic sign in intracranial neoplasms is discussed by MCKENDREE and FEMIER (*Arch. Neurol. and Psychiat.*, 1927, **17**, 44) in a review of 100 cases. The authors found this symptom present in 32 of the cases reviewed. The difficulty of differentiating between epidemic encephalitis and brain tumor in some cases was noted. They found that somnolence is not valuable as a differential point in regard to anatomic region involved, the age or the type of the tumor. It was most constantly found in cases exhibiting marked internal hydrocephalus. They believe that increased intracranial pressure, with or without ventricular distention, operates in producing this symptom.

Crime and its Causes.—TAIT (*J. Abnor. and Social Psychol.*, 1926, **21**, 234) believes that mentally defective and psychopathic individuals appear more frequently in one court, not because they commit more crimes, but because they are apprehended oftener. He describes the activity of certain social organizations interested in the investigation of crime, and believes there is a causal connection between the increase in crime and the reform measures for the management of criminals advocated by such organizations. The home, where the habits which should inhibit the primitive instincts that are frequently antisocial are established, has disintegrated with the externalizations of society. He believes crime can be controlled only by appropriate treatment in the form of punishment.

Tuberculoma of the Brain: its Incidence among Intracranial Tumors and its Surgical Aspects.—VAN WAGENEN (*Arch. Neurol. and Psychiat.*, 1927, **17**, 1), in a report from Dr. Cushing's Clinic, summarizes surgical experiences with intracranial tuberculomas. His report covers 17 cases: 6 cases were exposed and extirpation accomplished or attempted; 8 cases in which a lesion was not exposed or removed, but the diagnosis was verified at autopsy; 3 cases in which the presumed tuberculoma was not verified. Although the extirpation of tuberculomas in the first group was accomplished, the patients uniformly succumbed several weeks following operation, usually due to terminal tuberculous men-

ingitis. Only 1 patient survived for a period of a year and finally died from the effects of an operation for peritoneal tuberculosis. The author justly concludes his report by questioning the advisability of an operation with this type of brain tumor. The article is also of interest in that it indicates that previous statistics regarding the occurrence of tuberculoma in the brain were inaccurate. In a series of 1000 verified tumors only 1.4 per cent were of this type. Permanent recoveries are exceedingly rare. These tumors usually are located in the cerebellum or brain stem.

PATHOLOGY AND BACTERIOLOGY

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A Study of the Pathologic Changes in Scarlet Fever.—An anatomic-pathologic investigation of 32 cases of scarlet fever carried out by SYSAK (*Virchow's Arch. f. path. Anat.*, 1926, **259**, 647) stresses the relationship of the disease to glomerular and interstitial nephritis, to fat and iron depositions, and he discusses whether the streptococcus is the etiologic factor or a biologic accompaniment of the causative agent. He made blood cultures from 64 autopsy cases and found only 4 without bacteria, and in every positive case streptococcus was found alone, except where staphylococcus was present as a contaminant. Like many of the recent workers, represented by Lubarsch, he believed he found great variations in the streptococcus, dependent upon their environment, such as a loss of hemolysis, parallelling a return of the power to ferment mannite and a change of the hemolytic strain into a nonhemolytic after intraperitoneal inoculation into a mouse. The author found that on culture all the variations were of a minus order, as illustrated by a loss of virulence. On histologic section the deposition of iron was found in the spleen and tongue, but not in the pancreas. The fat was mostly in the form of cholesterol esters and was present in the heart in 50 per cent, more often in the spleen in phagocyting cells, also in the pancreas, liver, tongue and testes. On the other hand, the adrenal cortex showed a marked depletion of the fat, the residuum being found in the zona glomerulosa. This impoverishment the author regards as indicating the low level of fat in the blood, and this may be the cause of death in scarlet fever as in other acute infections, that is, the fat loss produces a hypofunction of the adrenals. The degree of fat deposit was dependent upon the presence of complications and

their severity. Likewise the amount of round-cell infiltration was related to the superimposed infections, and it was found that the mast cell was particularly characteristic of the uncomplicated cases of scarlet fever. The kidney changes were localized largely in the loops of Henle and the convoluted tubules, seldom involving the pyramids. Hemorrhage was frequent, and the primary changes specific to the disease were inserstitial and the exudative glomerular changes were consequent upon complications or a congenitally vulnerable organ. The pathologic process of scarlet fever is largely in the lymph system and the mast cell is the significant cell in the "perivascular granulomas" which are characteristic of this acute exanthem.

The Venereal or Inguinal Granuloma.—This infective disease has long been recognized in the East Indies and in America, but is practically unknown in Europe. GOLDZIEHER and PECK (*Virchow's Arch. f. path. Anat.*, 1926, **259**, 795) report from their New York clinic a number of cases showing an infective process involving the genitals and environs. The incubation period of these cases was about three weeks. The first appearance is a subcutaneous hard, brawny swelling, which frequently progresses to ulceration. This may persist as a chronic inflammation, lasting in one case as long as twenty-six years. The lesion appears as a flat, definitely marginated swelling, somewhat cupped in contour and extending centrifugally from the primary site on the genitals. The surface of the granuloma bleeds readily and an abundant watery exudate is formed which often becomes purulent. It also often becomes painful. The infiltrative cells are mainly neutrophils and eosinophils, but the more characteristic forms are plasma cells and large mononuclears with a waxy protoplasm, the latter being frequently the predominant type. These plasma and large mononuclear cells are similar to those described by Mikulicz, as found in rhinoscleroma, both being phagocytic; but the latter localizes on mucous membranes rather than on the skin surface. In the granulomas a pleomorphic organism was seen which was difficult to identify, but 5 of the 7 cases gave bacterium on culture. This bacterium appeared to belong to the Friedländer group, but was distinctive from it in its lack of capsule and in the abundant fat produced, which gave the cultures the odor of rancid butter. It ranged in appearance from a coccoid to a bacillary form with metachromatic granules. Complement-fixation and agglutination tests further differentiated the granuloma organism from the Friedländer bacillus and skin tests and vaccine produced immunities supporting the claim that it is the etiologic factor in inguinal granuloma. They found that the intravenous injections of tartar emetic, used for a sufficient period, was a specific remedy for the condition.

Auricular Endocarditis of Rheumatic Origin.—MacCallum, in 1924, drew attention to certain changes in the wall of the left auricle in rheumatic disease of the heart. They consisted in scarlike thickened patches, histologically showing cellular infiltration and large Aschoff bodies. Now VON GLAHN (*Am. J. Path.*, 1926, **2**, 1) reviews 31 cases of rheumatic valvular endocarditis and finds in 9 of them similar involvement of the left auricle. In 1 of these the right auricle was likewise affected; the whole 9 showed left auricular endocarditis. In

the gross, the changes usually occupied a small area just above the posterior leaflet of the mitral valve. This was marked by low, irregular ridges closely crowded together in a furrowed appearance. The surface may be smooth and glistening or roughened by tiny, dull, yellowish flecks. The older lesions are grayer and translucent. More marked cases show flat or delicately ridged plaques of yellow color in many parts of the auricle. In the later stages deposits of calcium occur in the superficial parts. Histologically, large accumulations of small mononuclear cells, many polymorphonuclears and a few eosinophils are found in the outer half of the endocardium. More striking still are collections of large cells with a faintly blue cytoplasm with oval, occasionally slightly lobed or stellate nuclei rather vesicular in character. They resemble the large cells that form Aschoff bodies in the myocardium. These cells often take up positions perpendicular to bands of hyalin-like material which lie in the elastic connective-tissue layer. The endothelium over the sites of these changes is usually intact, at other times a thin layer of fibrin appears on the surface. In the acute stages edema and fibrin in varying amounts separate the elastic fibers. Bacteria have not been demonstrated. Healing and repair occurs by fibrosis; the characteristic cells disappear and calcium not infrequently is present.

HYGIENE AND PUBLIC HEALTH

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Community Responsibility of Hospitals.—LEWINSKI-CORWIN (*Pub. Health Repts.*, 1926, **41**, 605) discusses certain points in the responsibility of "community hospitals," which are defined as hospitals from which "no profit can come to the hospital corporation." Policy: This will be based upon: (1) Morbidity prevalence of the community; (2) extent and character of services already available; (3) proportion of private, semiprivate and ward services; also there should be considered the care of outpatients, convalescents and chronic cases. Discharge of implied moral obligation: Professional service—attending, resident and nursing are to be determined on the basis of merit and no negligence, discourtesy or discrimination are to be tolerated. High type of performance: The important feature which differentiates the treatment in the hospital from that in the patient's home is the opportunity it offers for organized and supervised teamwork, for critical analysis of

the performance and for the advancement of the standards of medical education and practice in the community. This assurance to the community that the practice of medicine in the hospital is of the highest type attainable and that it sets the pace and promotes the best type of general practice in the community constitutes the civic responsibility of the hospital, which is of equal importance with that of the actual care of the sick within the hospital. Broader hospital opportunities for physicians: The physicians of the country must be supplied with opportunities for periodic contact with the best hospital practice. This is not an argument for "open" hospitals but for better utilization of the facilities of "closed" ones. The responsibility for training interns is mentioned. Delimitation of responsibility for nurse training: The obligation here is met by providing the best possible facilities for training, by inculcating a spirit of genuine service, and by making living and working conditions as satisfactory as possible. More interest should be taken in the training of "nurse attendants," duties of which require less education and less training than for registered nurses. Availability of hospital facts: The annual report should deal with the services rendered—it should show what the hospital has accomplished, not be merely a collection of medical statistics. It should be directed to the laity. Need of morbidity statistics. The vast reservoir of hospital statistics is not used to the best advantage of the community. A central bureau in large cities is advocated, with statistical service available to member hospitals. The units should be strictly comparable. Provisions for institutional convalescence and for the reclamation of the "chronics:" The importance of convalescent care is stressed and provision should be made to have it institutional in many cases. The chronic cases are inadequately cared for at present. There is a need for institutions for the chronically but not hopelessly ill who so often could be salvaged but who are likely to become victims of charlatans and cults. Provision for contagious disease isolation: Isolation units are required to meet emergencies in contagious diseases. Participation in health promotion: Periodic medical examinations and other health measures should be promoted.

Inherited Immunity in Tuberculosis.—CARTER (*Am. Rev. Tuberc.*, 1926, **13**, 373) states that in a comparison and study of some 5000 white patients at Catawba and Blue Ridge Sanatoria and 1700 colored patients treated under the same conditions at Piedmont Sanatorium results obtained in the whites are persistently better than the results shown for the colored. The mulatto negro also shows better results than those in the negro, but not as good as those in the white. The average age of persons treated is greatest in the white and least in the black. The mulatto occupies the middle ground. In the average age at death the results are like the former, highest in the white and lowest in the black race. The greatest incidence of tuberculosis occurs under thirty years of age in the black, next in the mulatto and least in the white. Over thirty the order is reversed. Environment may account for the difference between the black and white races, but this cannot be said of the mulatto and black. The conclusions drawn are that this better resistance, in the instances of the whites and mulattoes, is due to an inherited immunity from an ancestry that has accumulated that

immunity through contact with tuberculosis. The white races transmitting to the mulatto a part of stronger immunity accumulated through longer contact, this transmitted immunity plus that acquired by the mulatto gives him a better resistance to tuberculosis than the black whose immunity has been accumulated entirely by him since being in contact with civilization and almost entirely in the last seventy-five years since freedom has thrown him in contact with crowded centers of population.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 21, 1927

The Effect of Industrial Waste Gases on Plants.—RODNEY H. TRUE (from the Department of Botany, University of Pennsylvania). The development of industries in agricultural or forested areas sometimes gives rise to important problems in plant physiology and pathology. Several classes of industrial wastes have been found to be harmful to plant and animal life. Smelters sometimes give off mineral dusts that go into solution after they have settled on vegetation and cause injury to the plants and to animals grazing on them. Lead has been connected with one such case. The non-toxic dust from cement factories has been known to accumulate on the leaves of fruit trees and probably of other plants also to such an extent as to reduce the light supply to the chlorophyll-containing tissue and in some cases to block the stomata more or less completely.

Acid mists, in which sulphurous and sulphuric acids are borne in solution in water particles may be driven by air currents to considerable distances and when repeated often enough cause harm to plants. Such mists are sometimes irritating to the throat and cause an impulse to cough. Gases are sometimes given off in sufficient quantity to cause injury to plants. SO_2 is most frequently met with. This gas can be smelled in a concentration of from 3 to 5 or more parts per million according to the training and sensitiveness of the individual. This concentration is always potentially injurious to vegetation. If the "stream" of gas continues to lie across a given area for more than a brief period, or if repeated often enough injury is likely to occur. Ten parts per million give a marked odor of burning sulphur and is highly dangerous to plants. Plants vary widely in susceptibility to this gas in respect to the species in general, in respect to the stage of development and in respect to different parts of the plant. In most cases the older leaves are more sensitive to SO_2 than buds and younger leaves. Illuminating gas is also injurious to most plants; CO may easily reach harmful concentrations. Ethylene, sometimes used to enrich illuminating gas, produces striking results in some plants at great dilution. Buds

of carnation flowers will not open in an atmosphere containing 1 part per million and flowers already open will "go to sleep" after 12 hours of exposure. Sweet pea seedlings, grown in complete darkness, undergo strange distortions in 1 part per 10 million parts of air. Castor oil plants change the position in which the leaves are held in a like dilution. Ethylene tends to cause the disappearance of chlorophyll from green structures and has been used to hasten the development of yellow color in green lemons. It has also been found to cause celery to bleach rapidly when 1 to 10 parts are used in 10,000 parts of air.

The Relationship of Basal Metabolism to the Output of the Normal Urinary Pigment.—D. L. DRABKIN (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). The experimental results of a comprehensive study of the normal urinary pigment, "urochrome" (*J. Biol. Chem.*, 1926, **40**, 68), have led the writer to conclude that the quantity of pigment output is essentially independent of the diet and directly proportional to the basal metabolism (as calculated from the surface area in the normal rat, dog and man). The ability to markedly increase the output of pigment by increasing the rate of basal metabolism with such agents as thyroxin suggested the desirability of supplementing the experimental evidence by a study of pathologic individuals, especially those with diseases characterized by abnormal heat production (Graves' disease, fevers, and so forth). In order to interpret clinical data correctly it was essential to have some idea of the quantity of pigment eliminated by normal subjects. The fact that the pigment output was directly proportional to the surface area in many normal subjects of widely varying sizes (including three different species) was brought out by plotting the output of pigment against the surface area. This chart was utilized for deriving the normal pigment value of the particular individual under observation. A new series of cases, including 10 patients with Graves' disease, 1 with leukemia and 3 with lobar pneumonia, has been intensively studied, under controlled conditions. The pigment output was determined colorimetrically upon twenty-four-hour urine specimens (the reliability of collections being checked up by creatinine determinations). The determinations in all instances were upon consecutive days, in some cases over hospitalization periods two to three months long. In the Graves' disease and leukemia cases, metabolism determinations were made from time to time so as to permit a comparison of changes in output of pigment and metabolic rate.

In the exophthalmic goiter patients a distinct parallelism of the per cent increase in urinary pigment output and in basal metabolic rate was found. In a case which proved resistant to therapy both pigment output and basal metabolism persisted at levels far above normal. In another patient, where response to treatment was clinically apparent, and in whom the basal metabolism gradually fell towards normal, the pigment output also fell. In several individuals, after thyroidectomy, the urinary pigment fell to the normal or, indeed, somewhat below the calculated normal level. In the leukemia case, the relationship of pigment output and basal metabolism was similar to that observed in the thyroid patients. During the pyrexic stage of pneumonia the output of the urinary pigment was above normal, although the magnitude of the increase was of a lower order than in severe exophthalmic

goiter. In pneumonia urines extraneous pigments, such as urobilin and hematoporphyrin, were found to be excreted in appreciable and varying quantities so that they had to be removed in order to obtain a correct value for the normal urinary pigment output.

The data obtained from these carefully controlled clinical cases have fortified the conclusions, which the writer has reached upon the basis of his experimental studies. The output of the normal pigment of the urine is probably proportional to the intensity of the endogenous metabolism.

The clinical cases were supplied through the coöperation of Dr. Nellis B. Foster and his staff at the New York Hospital, Cornell University Medical School.

Anatomic Changes in the Kidneys of Rabbits following Administration of Novasurol and Salyrgan.—S. P. REIMANN and F. WINKELMANN (from the Research Institute of the Lankenau Hospital, Philadelphia). Novasurol, first used as an antiluetic measure, was found to possess marked diuretic properties. Certain disadvantages led to the production of salyrgan which contains approximately the same amount of mercury, 35 per cent, but is apparently less toxic. The chief mode of action of both is the production of a water and salt diuresis, probably by action on both the tissues and the kidneys. Since they contain mercury, they must be administered with caution; the field of usefulness is in cardiac edema with minor changes in the kidneys. Chemical studies can be found in the literature. Given to rabbits, the drugs produce a typical mercurial tubular nephritis with necrosis, disintegration and calcification in the tubules, especially the convoluted tubules and the ascending limbs of Henle's loop. The changes begin on the second to third day. Rabbits were killed at daily intervals after administration of the drug. Some animals died from the effects of overdosage in eight to ten days. Only animals in which preliminary functional tests had shown normal kidneys were used. The dose administered was relatively three to four times that used clinically.

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